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Transtracheal Augmented Ventilation for Chronic Severe Respiratory Disease

Evaluation of Automode with the Siemens Servo 300A Ventilator in a Porcine Model

Randomized, Controlled, Clinical Trial of a Chemically-Reactive Heated Humidifier

Nebulization of Budesonide Suspension vs Terbutaline Solution into a Neonatal Ventilator Circuit

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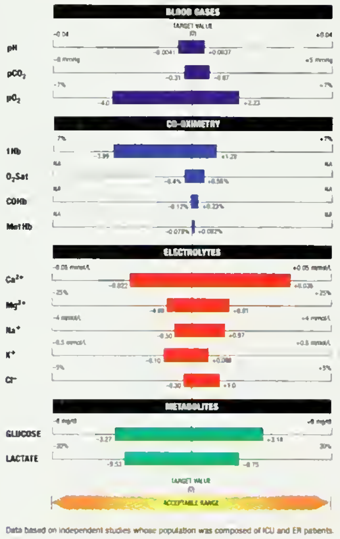

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Routine Screening for Lung Cancer? Maybe Someday, but Not Yet— Frame PS. JAMA 2000 Oct 18;284(15):1980-1983.

Pet Ownership and Asthma Morbidity—Simpson AJ, Matusiewicz SP, Greening AP, Crompton GK. Respir Med 2000 Jan;94(1):91-92.

Substance Abuse and Acute Asthma (review, tutorial)—Corbridge T, Cygan J, Greenberger P. Intensive Care Med 2000 Mar;26(3):347-349.

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CFC Transition: The Emperor's New Clothes—Each Class of Drug Deserves a Delivery System that Meets Its Own Requirements—Everard ML. Thorax 2000 Oct;55(10):811-814.

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Direct-to-Consumer Advertising of Prescription Drugs (op-ed)—Kravitz RL. West J Med 2000 Oct;173(4):221-222.

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Combination Therapy for Pulmonary Hypertension: A Glimpse into the Future? (editorial)— Channick RN, Rubin LJ. Crit Care Med 2000 Mar;28(3):896-897.

Red Blood Cell Transfusion in the Intensive Care Unit (review, tutorial)—Sherk PA, Granton JT, Kapral MK. Intensive Care Med 2000 Mar;26(3):344-346.

Changing Heat and Moisture Exchangers After 96 Hours Rather Than After 24 Hours: A Clinical and Microbiological Evaluation—Thomachot L, Boisson C, Arnaud S, Michelet P, Cambon S, Martin C. Crit Care Med 2000;28(3):714-720.

OBJECTIVE: The aim of this study was to determine whether changing heat and moisture exchangers (HMEs) every 96 hrs rather than 24 hrs would affect their efficacy to preserve the heat and moisture of inspiratory gases. The impact of a prolonged use of the HME on its microbial colonization was also assessed. DESIGN: Prospective cohort observational study. SETTING: Intensive care unit of a university hospital. PATIENTS: Thirteen consecutive patients with no previous history of respiratory disease requiring controlled mechanical ventilation with an HME for > 4 days were evaluated. INTERVENTIONS: The same HME was used for 96 hrs in each patient. MEASUREMENTS AND MAIN RESULTS: In each patient, during the inspiration phase, the following measurements were performed: peak and mean airway pressures, mean values of temperature, and relative and absolute humidity of inspired gases. In each patient, measurements were performed after 1 hr of HME use and then daily up to the fourth day. On days 1 and 4, microbiological samples were obtained from the patients' bronchial secretions and the ventilator side of the HME. After 96 hrs of ventilation with the same HME, tracheal tube occlusion was never observed. Using the same HME for 96 hrs rather than 24 hrs did not affect its technical performances: temperature at 24 hrs: 32.2 ± 1.5 ° C (90.0 ± 34.7 ° F), at 96 hrs: 32.1 ± 1.6 C (89.8 ± 34.9 ° F); relative humidity at 24 hrs: 97.9 ± 2%, at 96 hrs: 98.1 ± 1.7%; absolute humidity at 24 hrs: 33.1 ± 2.4 mg H_2O/L, at 96 hrs: 33.0 ± 2.5 mg H_2O/L. This analysis was based on a total of 312 measurements performed on the 13 patients. Peak and mean airway pressures did not change during the 96-hr study period, with identical tidal and minute volumes in the study patients. On day 1, ten patients had a positive culture of their tracheal secretions at a colony count of ≥ 10^3

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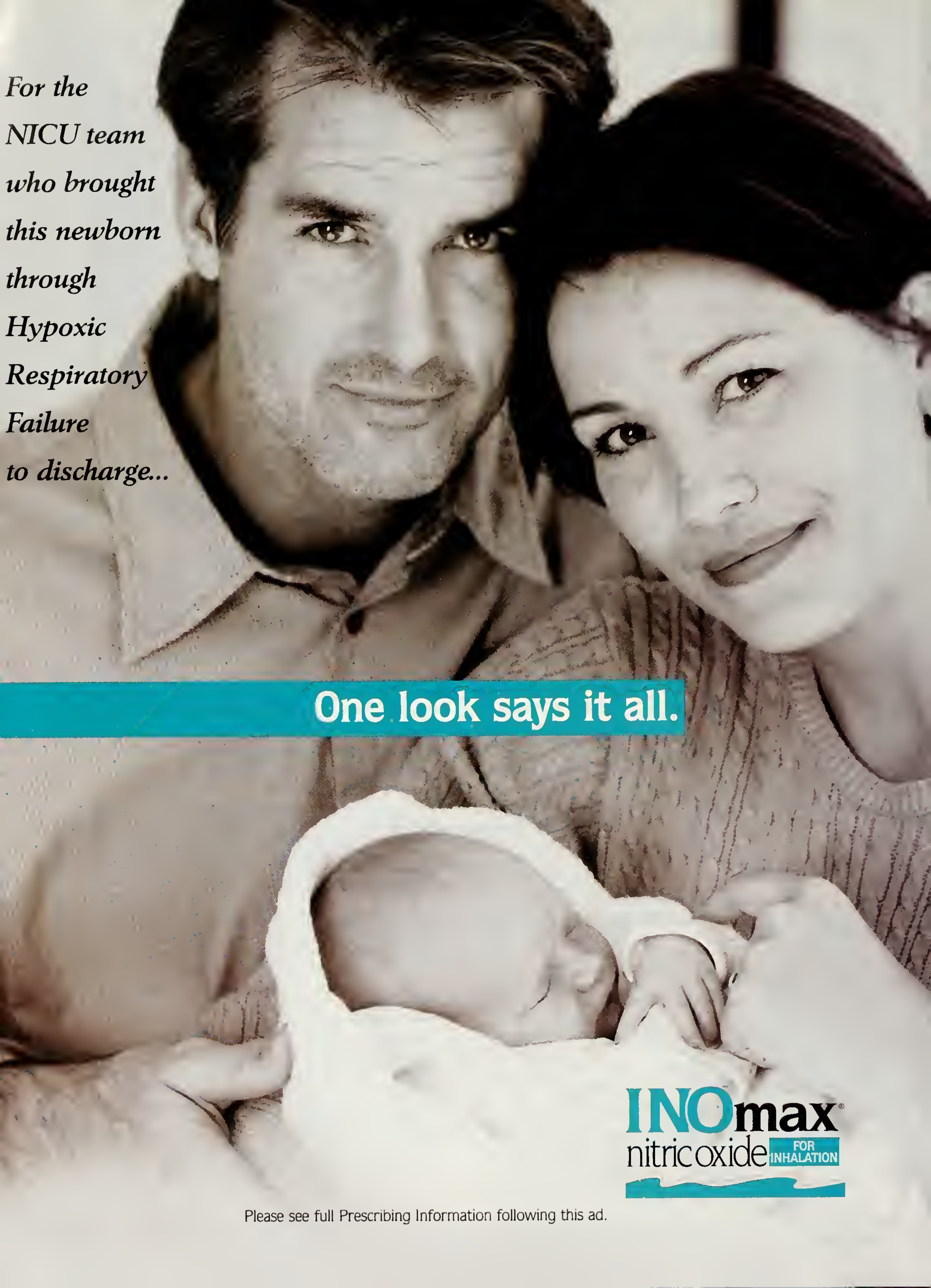
colony forming units/mL. After 96 hrs of use with the same HME, only seven patients had a positive culture of their tracheal secretions. Cultures from the ventilator sides of the HMEs were all sterile (13/13) after 96 hrs of use. CONCLUSIONS: In patients free from previous chronic respiratory disorder and ventilated for neurologic reasons, changing the HME after 96 hrs rather than 24 hrs did not affect its technical performance in terms of heat and water preservation of ventilatory gases. There is also some indirect evidence of very little, if any, changes in the HME resistance. No bacterial colonization of the ventilator sides of the HMEs was observed after 96 hrs of use. However, other large clinical trials should be undertaken to confirm the safety of extending the time between HME changes.

Effect of Nasal-Valve Dilation on Obstructive Sleep Apnea—Schönhofer B, Franklin, KA; Brünig H; Wehde H, Köhler D. Chest 2000; 118(3):587-590.

Objective: Nasal-valve dilation reduces nasal resistance and increases air flow. It is possible that this mechanism prevents hypopharyngeal collapse and sleep apneas. We investigated the effect of a plastic device (Nozovent; Prevancure AB; Västra Frölunda, Sweden)—which dilates the nasal valve—on patients with obstructive sleep apnea (OSA). Design: Prospective interventional study. Subjects: Twenty-six consecutive patients with OSA were included (22 men; mean ± SD age, 54.8 ± 11.3 years; respiratory disturbance index [RDI], 34.4 ± 18.5 events/h; body mass index, 31.6 ± 5.7 kg/m^2). Intervention: The nasal dilator was inserted during sleep into the nares and fitted to exert a dilating force on the nasal valves by means of its elasticity. Measurements: Polysomnographic studies were performed before and after 1 month of treatment. A responder is defined as one with a reduction in RDI to < 50% of the baseline value and RDI of ≤ 10 events/h during treatment. Results: Five patients dropped out. As a result, only 21 patients were analyzed. Four patients responded, and 17 patients were nonresponders. In the whole population, neither the mean values for respiration during sleep nor sleep staging changed significantly with the device. Conclusions: The investigated nasal dilator had no effect on sleep-related breathing disorders in patients with moderate to severe OSA. The reduction in nasal resistance does not prevent hypopharyngeal obstruction.

Hepatopulmonary Syndrome: A Prospective Study of Relationships between Severity of Liver Disease, P_{aO_2} Response to 100% Oxygen, and Brain Uptake After ^{99m}Tc MAA Lung Scanning—Krowka MJ, Wiseman GA, Burnett OL, Spivey JR, Therneau T, Porayko MK, Wiesner RH. Chest 2000;118(3):615-624.

Background: Because of the spectrum of intrapulmonary vascular dilation that characterizes hepatopulmonary syndrome (HPS), P_{aO_2} while breathing 100% oxygen varies. Abnormal extrapulmonary uptake of ^{99m}Tc macroaggregated albumin (MAA) after lung perfusion is common. Goal: To describe relationships between (1) severity of liver disease measured by the Child-Pugh (CP) classification; (2) P_{aO_2} while breathing room air (RA) and 100% oxygen on 100% oxygen; and (3) extrapulmonary (brain) uptake of ^{99m}Tc MAA after lung scanning. Methods and patients: We prospectively measured P_{aO_2} on RA, P_{aO_2} on 100% oxygen, and brain uptake after lung perfusion of ^{99m} Tc MAA in 25 consecutive HPS patients. Results: Mean P_{aO_2} on RA, P_{aO_2} on 100% oxygen, P_{aCO_2} on RA, and ^{99m} Tc MAA brain uptake were similar when categorized by CP classification. Brain uptake was abnormal (≥ 6%) in 24 patients (96%). Brain uptake was 29 ± 20% (mean ± SD) and correlated inversely with P_{aO_2} on RA (r = -0.57; $p < 0.05$) and P_{aO_2} on 100% oxygen (r = -0.41; $p < 0.05$). Seven patients (28%) had additional nonvascular pulmonary abnormalities and lower P_{aO_2} on 100% oxygen (215 ± 133 mm Hg vs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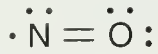
List No. 300-200.00

INOmax™(nitric oxide) for inhalation
100 and 800 ppm (parts per million)

DESCRIPTION

INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



CLINICAL PHARMACOLOGY

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces pulmonary vasodilation.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

Effects on Pulmonary Vascular Tone in PPHN: Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

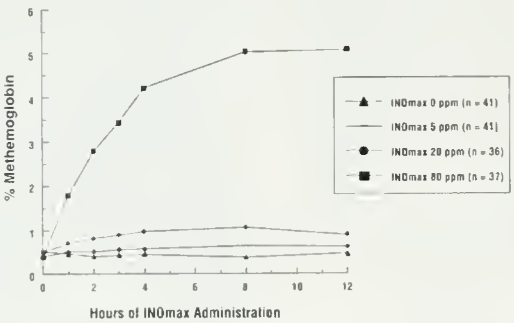
PHARMACOKINETICS

The pharmacokinetics of nitric oxide has been studied in adults.

Uptake and Distribution: Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

Metabolism: Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration–time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1
Methemoglobin Concentration-Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.

Elimination: Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

CLINICAL TRIALS

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration [F_iO_2] x 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 (see CLINICAL PHARMACOLOGY).

(i) NINOS study: The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10-20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 1.

Table 1
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO [a,b]	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

[a] Extracorporeal membrane oxygenation
[b] Death or need for ECMO was the study's primary end point.

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups (see ADVERSE REACTIONS). Follow-up exams were performed at 18-24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

(ii) CINRGI study: This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH <7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 2.

Table 2
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO [a,b]	51/89 (57%)	30/97 (31%)	< 0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[a] Extracorporeal membrane oxygenation
[b] ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups (see ADVERSE REACTIONS).

INDICATIONS

INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

CONTRAINDICATIONS

INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

PRECAUTIONS

Rebound

Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

Methemoglobinemia

Methemogloginemia increases with the dose of nitric oxide. In the clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours.

Elevated NO_2 Levels

In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

Drug Interactions

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. In particular, although there are no data to evaluate the possibility nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals to evaluate the carcinogenic potential of nitric oxide have been performed. Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility or harm to the developing fetus.

Pregnancy: Category C

Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

Pediatric Use

Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). No information about its effectiveness in other age populations is available.

Nursing Mothers

Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

ADVERSE REACTIONS

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage; Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse events with an incidence of at least 5% on INOmax in the CINRGI study, and that were more common on INOmax than on placebo.

ADVERSE EVENTS IN THE CINRGI TRIAL

Adverse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 *(10%)*	13 *(13%)*
Withdrawal	9 *(10%)*	12 *(12%)*
Atelectasis	8 *(9%)*	9 *(9%)*
Hematuria	5 *(6%)*	8 *(8%)*
Hyperglycemia	6 *(7%)*	8 *(8%)*
Sepsis	2 *(2%)*	7 *(7%)*
Infection	3 *(3%)*	6 *(6%)*
Stridor	3 *(3%)*	5 *(5%)*
Cellulitis	0 *(0%)*	5 *(5%)*

OVERDOSAGE

Overdosage with INOmax will be manifest by elevations in methemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

DOSAGE AND ADMINISTRATION

Dosage

The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but those patients did not then improve on the higher dose. As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm, doses above this level ordinarily should not be used.

Administration

Additional therapies should be used to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high frequency oscillatory ventilation.

The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies (see CLINICAL STUDIES).

INOmax should be administered with monitoring for PaO_2, methemoglobin, and NO_2.

The nitric oxide delivery systems used in the clinical trials provided operator-determined concentrations of nitric oxide in the breathing gas, and the concentration was constant throughout the respiratory cycle. INOmax must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. The INOvent™ system and other systems meeting these criteria were used in the clinical trials. In the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms. The system should be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide, such as INOcal™. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. Oxygen levels should also be measured.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

The INOmax dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax. Discontinue/wean cautiously.

HOW SUPPLIED

INOmax (nitric oxide) is available in the following sizes:

Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)
Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

CAUTION

Federal law prohibits dispensing without a prescription.

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391 ± 137 mm Hg; $p < 0.007$). Eight patients (32%) died. Mortality in patients without coexistent pulmonary abnormalities was associated with greater brain uptake of ^{99m}Tc MAA (48 ± 18% vs 25 ± 20%; $p < 0.04$) and lower P_{aO_2} on RA (40 ± 7 mm Hg vs 57 ± 11 mm Hg; $p < 0.001$). Conclusion: The degree of hypoxemia associated with HPS was not related to the CP severity of liver disease. HPS patients with additional nonvascular pulmonary abnormalities exhibited lower P_{aO_2} on 100% oxygen. Mortality was associated with lower P_{aO_2} on RA, and with greater brain uptake of ^{99m}Tc MAA.

Quality of Spirometry Test Performance in Children and Adolescents: Experience in a Large Field Study—Enright PL, Linn WS, Avol EL, Margolis HG, Gong Jr H, Peters JM. Chest 2000;118(3):665-671.

Study objective: To determine the ability of children and adolescents to meet the American Thoracic Society (ATS) goals for spirometry quality that were based on results from adults. Design: Observational. Participants: More than 4,000 public school students, ages 9 to 18 years. Measurements: Spirometry was performed annually for 3 years, with the recording of maneuver quality measures of forced expiratory time, end-of-test volume, back-extrapolated volume, and time to peak expiratory flow (PEFT), and the recording of differences between best and second-best FVC, FEV_1, and peak expiratory flow (PEF) values. Results: Regression analyses showed significant influences of participant age, gender, ethnicity, size, clinical status, and previous testing experience, as well as differences among individual test technicians. In general, these influences were small and explained little of the variance in performance. On average, children with a history of asthma or wheeze performed better quality spirometry than did others. Only PEFT improved significantly from year to year. Overall, only 15% of girls' tests and 32% of boys' tests met the PEFT criterion derived from adults in the Lung Health Study. Conclusion: Most of the children met adult-based ATS goals for spirometry test performance. Age group-specific criteria are needed to ensure adequately fast PEFT and reproducible PEF values.

Correlation of Changes in Quality of Life After Lung Volume Reduction Surgery with Changes in Lung Function, Exercise, and Gas Exchange—Leyenson V, Furukawa S, Kuzma AM, Cordova F, Travaline J, Criner GJ. Chest 2000;118(3):728-735.

Study objectives: To evaluate correlations between improvement in quality of life (QOL) in patients with severe COPD before and after they undergo lung volume reduction surgery (LVRS) with changes in pulmonary function tests, gas exchange, exercise performance, and alterations in medical management. Design: Case-series analysis. Setting: University hospital. Patients: Forty-two patients (mean [± SD] age, 56 ± 8 years; 53% women) with severe airflow obstruction (FEV_1, 0.62 ± 0.2 L), and moderate to severe hyperinflation (total lung capacity [TLC], 6.9 ± 1.7 L). Intervention and measurements: All patients underwent bilateral LVRS via median sternotomy. Measurements of lung function, symptom-limited cardiopulmonary exercise testing, the total distance the patient was able to walk in 6 min in a corridor, and sickness impact profile (SIP) scores were made before and 3 months after LVRS. SIP scores are inversely proportional to the level of function and QOL. Results: Compared to baseline, FEV_1 increased (0.87 ± 0.3 vs 0.62 ± 0.2 L, respectively; $p < 0.01$) while residual volume significantly decreased (3.2 ± 1.8 vs 6.3 ± 1.2 L, respectively; $p < 0.004$) at 3 months post-LVRS. On cardiopulmonary exercise testing, values increased from baseline to post-LVRS for total exercise time (9.0 ± 2.2 vs 6.0 ± 1.5 min, respectively; $p = 0.045$), maximum oxygen uptake ($\dot{V}_{O_2}$) (16 ± 3 vs 11 ± 2 mL/kg/min, respectively; $p = 0.01$), and maximum minute ventilation ($\dot{V}_E$) (33 ± 9 vs 28 ± 5 L/min, respectively; $p = 0.03$). The percentage change in the oxygen cost of breathing ($\dot{V}_{O_2}/\dot{V}_E$ ratio) from low to high workloads during exercise was significantly lower after LVRS ($p = 0.002$). There was no significant change in oxygenation after LVRS (P_{aO_2}/fraction of inspired oxygen, 331 ± 27 vs 337 ± 39, respectively; $p = 0.76$), but P_{aCO_2} tended to be lower (41 ± 9 vs 48 ± 6 mm Hg, respectively; $p = 0.07$). Overall SIP scores were significantly lower after LVRS than before (8 ± 4 vs 15 ± 2, respectively; $p = 0.002$). Changes in SIP scores correlated with the change in $\dot{V}_{O_2}/\dot{V}_E$ ratio from low to high workloads, with patients having the smallest changes in $\dot{V}_{O_2}/\dot{V}_E$ ratio having the smallest changes in SIP scores after LVRS ($r = 0.6$; $p = 0.01$). Improved or lower SIP scores also tended to correlate with a reduction in residual volume/TLC ratio ($r = 0.45$; $p = 0.09$), and there was a linear correlation with a statistically significant Pearson r value with decreased steroid requirements ($r = 0.7$; $p = 0.001$). Moreover, changes in psychological SIP subscore tended to correlate with diminished oxygen requirements post-LVRS ($r = 0.45$; $p = 0.09$). However, there was no significant correlation between changes in SIP scores and routine measurements of lung function, exercise performance, or gas exchange. Conclusion: There is an association between an improvement in QOL and reduced hyperinflation after LVRS. Reduced hyperinflation may lead to more efficient work of breathing during exercise and, therefore, to an increased ability to perform daily activities. Changes in QOL scores correlate best with behaviorally based variables that directly affect the patient's well-being, such as systemic steroid administration.

Preliminary Observations of Transtracheal Augmented Ventilation for Chronic Severe Respiratory Disease

Kent L Christopher MD RRT, D Theron VanHooser MEd RRT, Susan J Jorgenson RN MSN, Les Winslett RPFT, Stephanie S Diehl RRT, David A Young PhD, Howard Shapiro PhD, and Thomas L Petty MD FAARC

OBJECTIVE: Evaluate the potential safety and efficacy of transtracheal augmented ventilation (TTAV), which is the transtracheal delivery of high flows of a humidified air-oxygen blend. METHODS: The first of 2 observational studies evaluated patients before and after a 3-month intervention with the nocturnal (Noc) administration of TTAV at 10 L/min. Resting physiologic studies evaluated standard low-flow transtracheal oxygen (LFTTO), TTAV, and breathing without transtracheal flow via mouthpiece (MP). Patients also underwent nocturnal polysomnography, bronchoscopy, ventilatory drive evaluation, and treadmill exercise. The second study assessed the safety of Noc TTAV for up to 60 months. Each study evaluated 15 different transtracheal patients with severe lung disease. RESULTS: Pleural pressure-time index and respiratory duty cycle were significantly lower ($p < 0.05$) when comparing MP to TTAV. TTAV contributed more ($p < 0.05$) than LFTTO to the total volume delivered to the lung ($\dot{V}_L$). Arterial blood gases and $\dot{V}_L$ were unaltered by TTAV. Sleep quality and nocturnal oxygenation with TTAV were similar to LFTTO, and Noc TTAV had no effect on ventilatory drive. Bronchoscopy showed no evidence of substantial injury. Treadmill exercise tests showed a longer exercise time ($p < 0.005$) and greater total work ($p < 0.05$) following Noc TTAV. During exercise, the changes in slope for heart rate and pH were less steep ($p < 0.05$) following Noc TTAV. The 3-month study and a long-term evaluation showed that Noc TTAV was well-tolerated and safe, with a reported high compliance. CONCLUSIONS: Patients with chronic hypoxemia and severe respiratory insufficiency may benefit from Noc TTAV. [Respir Care 2001;46(1):15–25] *Key words: transtracheal oxygen therapy, chronic respiratory insufficiency, chronic respiratory disease, chronic obstructive pulmonary disease, COPD, hypoxemia, ventilation, augmented ventilation.*

The benefits of long-term oxygen therapy have been well-defined.[1] In an attempt to improve and expand these benefits, the transtracheal method of continuous oxygen therapy was developed. Transtracheal oxygen therapy (TTO) has a number of advantages over the standard nasal cannula.[2–13] Oxygen flow requirements during rest and

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At the time of this study, Kent L Christopher MD RRT and Thomas L Petty MD FAARC were affiliated with the Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado. D Theron VanHooser MEd RRT, Susan J Jorgenson RN MSN, Les Winslett RPFT, and Stephanie S Diehl RRT were with Vencor Denver Hospital, Denver, Colorado. David A Young PhD was affiliated with the Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, Colorado. Howard Shapiro PhD was with the Department of Research and Development, HealthONE, Denver, Colorado.

This research was supported by HealthONE Grant 9012R, Vencor Denver Hospital, Denver, Colorado, and Bird Products Corporation, Palm Springs, California.

Kent L Christopher MD RRT is a co-inventor of the SCOOP Transtracheal Oxygen System. He received equity for licensing patents to the manufacturer (Transtracheal Systems). Dr Christopher is a scientific advisor to Transtracheal Systems. He is the inventor of transtracheal augmented ventilation technology and holds patents.

Susan J Jorgenson RN MSN presented part of the present research during the annual Open Forum at the 39th Annual Meeting and Exposition of the American Association for Respiratory Care, Nashville, Tennessee, December 11–14, 1993.

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exertion are significantly lower[2–4,9] and monthly bulk oxygen use is decreased.[5,9] Improved comfort, self-image, and ambulation with TTO result in high patient acceptance and 24-hour-a-day compliance.[3,6–9]

Initial reports[4,8] suggested that a major benefit of TTO was the ability to achieve adequate oxygenation with flows as low as 0.25–0.75 L/min. Subsequent clinical experience found that resting transtracheal flows in the range of 0.5 to 2.5 L/min are generally required to achieve adequate oxygenation in the typical patient on home oxygen. In contrast, a unique group of patients was encountered who had severe refractory hypoxemia[2] and needed much higher TTO flows, of up to 6 L/min, to achieve adequate oxygenation. Anecdotally, some of those individuals appeared to have reduced work of breathing (WOB) with the higher TTO flows.[2] We wondered whether flows in excess of 6 L/min might be of additional benefit with respect to reduced WOB or augmented ventilation.

In this investigation, we inquired whether higher flows of an oxygen and air blend would produce substantial physiologic benefits in patients who were previously receiving TTO at lower flows. We use the term transtracheal augmented ventilation (TTAV) to refer to a humidified mixture of air and oxygen administered at high flows (eg, 10 L/min.).

These observations aimed to more thoroughly evaluate the potential efficacy and safety of this new method for augmentation of ventilation. The purpose of the first of the 2 studies was to evaluate the effects of TTAV before and after 3 months of nocturnal support of 15 stable outpatients with mature transtracheal tracts and chronic hypoxemia due to severe respiratory insufficiency. We wanted to pursue 4 goals.

First, we aimed to determine if some of the described physiologic benefits of transtracheal gas delivery were flow-dependent beyond the range employed in previous studies,[3–11] that is, up to flows encountered with TTAV of 10 L/min.

The second goal was to determine if patients' physiologic responses to high TTO flows changed over 3 months of nocturnal treatment.

The third goal was to evaluate the safety and patient tolerance of nocturnal (Noc) TTAV over 3 months of therapy, particularly with respect to the appearance of the tracheobronchial mucosa and both nocturnal oxygen saturation and sleep quality. In addition, we questioned whether 3 months of Noc TTAV might have an effect on either exercise capacity or ventilatory drive in patients who had previously received only standard TTO therapy with lower flows.

The fourth goal was to gain information on the long-term safety and patient acceptance of Noc TTAV in the treatment of a second series of 15 outpatients with mature transtracheal tracts and chronic hypoxemia due to severe respiratory insufficiency.

Materials and Methods

Series of Evaluations Before and After 3 Months of Nocturnal Transtracheal Augmented Ventilation

Subjects. Fifteen medically stable outpatients with severe chronic respiratory insufficiency, mostly from advanced chronic obstructive pulmonary disease (COPD) and chronic hypoxemia, were evaluated. These included patients with COPD (11), interstitial lung disease (1), kyphosis (1), cystic fibrosis (1), and recurrent pulmonary emboli (1). Institutional review board approval and informed consent were obtained. At the start of our studies, each subject was already receiving low-flow transtracheal oxygen (LFTTO) via mature tracheocutaneous fistula. Entry data included arterial blood gas (ABG) measurement (ABL 330, Radiometer, Copenhagen, Denmark) on standard TTO therapy (SCOOP-1, Transtracheal Systems, Englewood, Colorado). In addition, spirometry (1070, Medical Graphics Corp, St Paul, Minnesota) was done according to the recommendations of the American Thoracic Society.[14]

Patients underwent a series of studies (Fig. 1) before and after a 3-month intervention with Noc TTAV. The first studies were designed to compare the resting physiologic response to low flow (LFTTO) and high flow (TTAV). Nocturnal polysomnography studies were done to evaluate conditions of LFTTO to TTAV. Ventilatory drive was assessed during hypoxic and hypercarbic challenges, and exercise was evaluated using a treadmill. Bronchoscopy was done to determine the potential effect of TTAV high flows on tracheobronchial mucosa. In addition, patients were clinically monitored in the home while receiving Noc TTAV therapy.

Resting Physiologic Response to Transtracheal Flow. During the day, subjects were randomly assigned to receive LFTTO and TTAV, and nontranstracheal oxygen delivery via mouthpiece (MP) in random order. With MP, the mouthpiece was attached to a one-way valve and a reservoir bag filled with an adjustable oxygen-enriched gas mixture. Oxygen flows were titrated (Model 3740, Ohmeda, Boulder, Colorado) to achieve a stable S_{pO_2} (oxygen saturation measured via pulse-oximetry) of 92–95% with LFTTO. The F_{IO_2} (fraction of inspired oxygen) was adjusted during MP and TTAV to achieve a similar saturation. Gas flow with TTAV was set at 10 L/min. Under conditions of TTAV, LFTTO, and MP, and after a 15-minute stabilization period, ABG samples were drawn via indwelling catheter.

With LFTTO, TTAV, and MP, flow at the mouth was then measured with a pneumotachometer. In addition, an esophageal balloon was placed to allow for measurements of esophageal pressure (CP-100, BICORE Monitoring Sys-

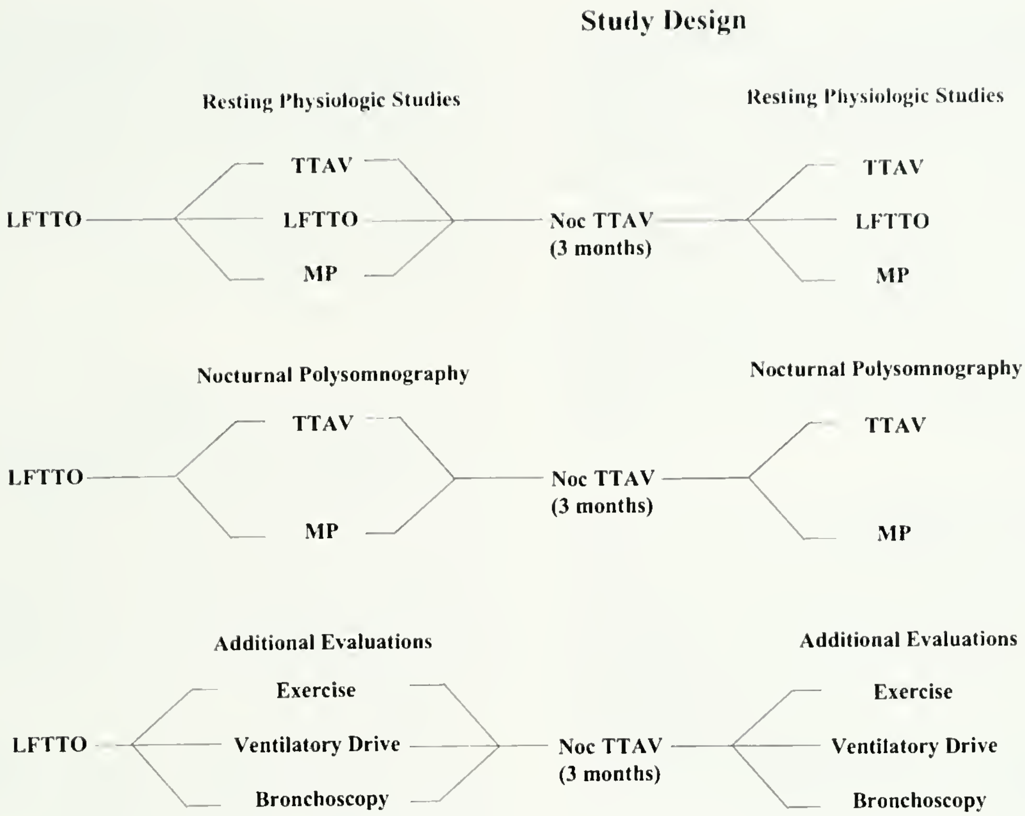

Fig. 1. Evaluations were done at baseline on low-flow transtracheal oxygen (LFTTO) and repeated following 3 months of nocturnal transtracheal augmented ventilation (Noc TTAV). During resting physiologic studies TTAV, LFTTO, and mouthpiece (MP) breathing in the absence of transtracheal flow were administered in random order. Nocturnal polysomnography was conducted on LFTTO and TTAV administered on two consecutive nights in a random fashion. Additional testing included treadmill exercise testing, assessment of ventilatory drive, and inspection of the tracheobronchial mucosa via fiberoptic bronchoscopy.

tems, Irvine, California). Data from the BICORE flow and esophageal pressure (P_{es}) signals were downloaded to a personal computer for data analysis through a customized software application (BICORE Monitoring Systems, Irvine, California). Utilizing the methods of Benditt et al,[11] data collected under conditions of LFTTO, TTAV, and MP were averaged for 10 consecutive breaths. Respiratory rate (f) and the respiratory duty cycle (ratio of inspiratory time to total time of respiratory cycle, or T_I/T_{TOT}) were calculated. The tidal volume inspired through the mouth (V_{TM}) × f defined the minute ventilation inspired via the mouth ($\dot{V}_M$). During LFTTO and TTAV, transtracheal gas flow was integrated over T_I and added to V_{TM} to yield the V_T delivered to the lung during inspiration (V_{TL}). The minute volume delivered to the lung during inspiration ($\dot{V}_L$) was calculated from f × V_{TL}. The pleural pressure-time index (PPTI) was calculated as described by Benditt et al.[11]

Nocturnal Polysomnographic Studies. Sleep studies were done in each patient's hospital room, using a portable system (Medilog 9200, Oxford, Clearwater, Florida) while the patients received Noc TTAV as compared to LFTTO as a control, in random order on 2 consecutive nights. Results were scored in the standard fashion,[15] and data regarding sleep efficiency, S_{pO_2}, and the presence or absence of sleep apnea were reported. The 2 nights of sleep studies were repeated in the same fashion following the 3-month Noc TTAV intervention.

Assessment of Ventilatory Drive. Mouth occlusion pressure was then measured (2001, Medical Graphics Corporation, St Paul, Minnesota), as previously described,[16] during MP conditions using both hypoxic and hypercarbic challenges.

Treadmill Exercise Study. A maximal graded exercise study was performed using a treadmill (T500, Burdick, Milton, Wisconsin), while each subject breathed under MP conditions. TTO administration during exertion has been shown to improve exercise capacity, and improvement is directly related to the transtracheal gas flow.[9] Therefore, transtracheal gas was not administered, so as to better assess the potential effect of the Noc TTAV intervention on exercise capacity. Serial ABG samples were drawn from an indwelling arterial catheter and continuous electrocardiograph tracings were recorded (E550, Burdick, Milton, Wisconsin). Speed and elevation were progressively increased until patients could no longer continue. Duration of exercise (minutes) and total work (joules) were calculated. During the post-Noc TTAV exercise evaluation, the increase in speed and elevation over time was reproduced from the pre-Noc TTAV intervention study. If the patient was able to exercise past the pre-Noc TTAV conditions, the final (and highest) pre-Noc TTAV speed and elevation treadmill settings were maintained until the subject could no longer continue. Exercise results following 3 months of TTAV were compared to results following previous therapy with LFTTO.

Fiberoptic Bronchoscopy. Each patient was placed on a nasal cannula and oxygen flows were titrated to maintain S_{pO_2} above 92%. Approximately 3 mL of lidocaine 1% was instilled into the trachea via the TTO catheter, and the TTO catheter was removed. A pediatric bronchoscope (Olympus PF 27M, Ultra Thin Fiberscope, Olympus America, New York, New York) was inserted into the trachea via the tracheocutaneous fistula. The tracheobronchial mucosa was inspected for the presence of hemorrhage, exudates, ulceration, or necrosis. Baseline results during LFTTO administration were compared to the post-Noc TTAV results.

Nocturnal Transtracheal Augmented Ventilation Administration and Monitoring during 3 Months of Treatment. A customized device (Bird Products, Palm Springs, California) was used to administer TTAV in the first series of subjects each night in the home, for 3 months, using flows of 10 L/min and F_{IO_2} established during baseline physiologic testing. The device consisted of an adjustable blender and flow meter attached to both an air compressor operating at 22 psi and a standard 22 psi stationary liquid oxygen reservoir (Mallinckrodt/Puritan-Bennett, St Louis, Missouri, or Cryogenics Equipment Division, Indianapolis, Indiana). The gas from the blender was delivered through an adjustable servo humidifier equipped with a heated wire circuit (Models BLD 17000 and BLD 19501, Bird Life Design Systems, Division of Bird Products, Palm Springs, California). The circuit was attached to a SCOOP-1 transtracheal catheter via a modified oxygen hose (Transtracheal Systems, Englewood, Colorado). During the day, patients used stationary and portable liquid oxygen sources to receive their previously prescribed resting and exercise flows. In the home, patients were closely monitored biweekly and on an as-needed basis by a single home care company (Pediatric Services of America, Denver, Colorado). The home care company inquired about compliance with TTAV and the patients' understanding and acceptance of the equipment. In addition, the home care company carefully inspected the equipment on a biweekly and as-needed basis, noting accuracy of set F_{IO_2} and flow rates. Subjects were given inservice training about nocturnal use of the TTAV system, but were not advised about daytime activity. Medication changes were kept at a minimum, and patients did not participate in a pulmonary rehabilitation program either immediately before or during the 3 months of TTAV.

Statistical Analysis

The differences between post-treatment and pre-treatment outcomes within patients for each outcome were tested between pairs of treatment groups by a two-tailed paired *t* test. A p value of 0.05 was set as the statistical significance level. For the resting physiologic testing, each treatment pair was evaluated by paired pre-treatment outcomes and separately for paired post-treatment outcomes. Statistical testing was performed by paired *t* tests. Statistical significance was also evaluated for each treatment outcome by Bonferoni's adjustment for multiple comparisons (setting the significance level at $0.05/3 = 0.017$).

For the sleep study, outcomes were analyzed by a model for a 2×2 crossover design.[17] Period and sequence effects were evaluated, whereas carry-over effects were assumed negligible because of the length of treatment. All tests were two-tailed, with $p < 0.05$ as the significance level.

The changes in heart rate and pH during the treadmill exercise were examined using the linear random effects model described by Laird and Ware.[18] This model is appropriate for repeated measures data, accounting for variability between patients as well as the variability between multiple observations of the same patient. Distinguishing between the 2 sources of variability provided a significantly better fit to the data (likelihood ratio test, $p < 0.001$). Linear regression lines provided the best fit for both variables for both groups (likelihood ratio tests, $p < 0.001$). Rates of increase pre-intervention versus post-intervention were examined by comparing slopes using Wald tests.[19]

All analyses were implemented with the SAS statistical software package (SAS STAT, 1996, Version 6.12, SAS Institute, Cary, North Carolina). Data are presented as mean ± 1 SD, unless otherwise indicated.

Long-Term Nocturnal Transtracheal Augmented Ventilation Using an Oxygen Enricher

After completion of the above studies, a second series of 15 TTO patients, also with severe chronic respiratory insufficiency, participated in a long-term follow-up while receiving Noc TTAV using a commercially available high-humidity oxygen enricher (OE Plus, Gulfstream Medical Products, Bedminster, New Jersey). Standard LFTTO was administered during the day using liquid oxygen. A home care company therapist (NMC Homecare, Denver, Colorado) carefully inspected the equipment monthly and on an as-needed basis, noting accuracy of set F_{IO_2} and flow rates. F_{IO_2} was adjusted to achieve an S_{pO_2} of 92–94%. If F_{IO_2} with the oxygen enricher was not adequate, supplemental oxygen was bled in using the stationary liquid oxygen source, and the total delivered gas flow was 10 L/min. Nocturnal oximetry was periodically monitored in the home. Patients were questioned about their acceptance and compliance with Noc TTAV. Data are given as mean ± 1 SD, unless otherwise stated.

Results

Series of Evaluations Before and After 3 Months of Nocturnal Transtracheal Augmented Ventilation

Subjects. Thirteen of the original 15 patients completed the first investigation. One patient was diagnosed with cancer during the study and was withdrawn because of the physical and emotional demands of cancer treatment. Another patient became more anxious with the testing protocols and the higher technology associated with TTAV, and the investigators encouraged the patient to withdraw. Table 1 shows the clinical data on the 13 patients who finished the study. Overall, subjects had been on TTO for a relatively long period of time (29 ± 26 mo). Patients had severe respiratory insufficiency without severe hypercarbia (arterial partial pressure of carbon dioxide 44 ± 7 mm Hg, range 37–54 mm Hg).

Resting Physiologic Response to Transtracheal Flow. Oxygen flow required to achieve an adequate S_{pO_2} with LFTTO during resting evaluations was 3.4 ± 2 L/min, and the F_{IO_2} required with TTAV ranged from 0.4 to 0.7 (data not shown). During pre-Noc TTAV and post-Noc TTAV studies, there were no significant differences in respiratory rate, pH, arterial partial pressure of carbon dioxide (P_{aCO_2}), or arterial oxygen saturation with LFTTO or TTAV, compared to the control MP conditions (Table 2).

Table 2 shows the results of PPTI and T_I/T_{TOT} measurements obtained before and after the 3-month trial of Noc TTAV. Both PPTI and T_I/T_{TOT} varied inversely with transtracheal flow. During both pre-Noc TTAV and post-Noc TTAV studies, both PPTI and T_I/T_{TOT} were significantly lower ($p < 0.05$) with TTAV than with the MP control. When adjusted for multiple comparisons, results remained significant except for post-treatment T_I/T_{TOT} (nominal $p = 0.039$). The values for LFTTO for both PPTI and T_I/T_{TOT} were less than with the MP control, but the differences were not significant. Table 2 shows the results of $\dot{V}_L$ data. There were no significant differences in the total volume delivered to the lung on inspiration through the control (MP) or with the mouth volume plus additional transtracheal insufflation (LFTTO and TTAV). However, the percent contribution of TTAV to $\dot{V}_L$ was significantly greater ($p < 0.05$) than the contribution of LFTTO to $\dot{V}_L$. In fact, TTAV contributed 45% of $\dot{V}_L$.

Table 1. Clinical Data

Age (y)	66 ± 11
Men/Women (n/n)	8/5
Time on TTO (mo)	29 ± 26
Lung Disease (n)	
COPD	9
Interstitial lung disease	1
Kyphoscoliosis	1
Cystic fibrosis	1
Pulmonary emboli	1
Spirometry Findings	
FEV_1 (L)	0.84 ± 0.4
FVC (L)	1.8 ± 0.8
FEV_1/FVC (%)	45 ± 16
Arterial Blood Gases*	
P_{aO_2} (mm Hg)	86 ± 21
P_{aCO_2} (mm Hg)	44 ± 7
pH	7.43 ± 0.03

Values are mean ± SD, where applicable
TTO = transtracheal oxygen
COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
*Obtained at rest on TTO (3.4 ± 2 L/min)
P_{aO_2} = arterial partial pressure of oxygen
P_{aCO_2} = arterial partial pressure of carbon dioxide

Nocturnal Polysomnographic Studies. Results with Noc TTAV were similar to the LFTTO control with respect to sleep quality. Sleep efficiency was not significantly different in the before and after studies for LFTTO (58.5% and 51.7%, respectively) or Noc TTAV (65.3% and 60.2%, respectively). None of the patients had sleep apnea. Anecdotally, patients noted that they had more difficulty sleeping in the hospital during the polysomnographic studies than they did on unmonitored Noc TTAV in the home. Nocturnal oxygen saturation measured via pulse oximetry was maintained above 90% with both LFTTO and TTAV.

Assessment of Ventilatory Drive. There were no significant differences with respect to pre-Noc TTAV and post-Noc TTAV measurement of $P_{0.1}$ (airway occlusion pressure at the first 100 ms after airway closure) with MP breathing during hypoxic and hypercarbic challenges (Table 3).

Treadmill Exercise Study. The total work achieved during exercise (Figure 2A) was greater ($p < 0.05$) and exercise time (Figure 2B) was longer ($p < 0.005$) during the

Table 2. Respiratory Mechanics and Arterial Blood Gas Values Obtained Before and After 3-Month Trial of Nocturnal TTAV

	MP		LFTTO		TTAV	
	Before	After	Before	After	Before	After
PPTI (cm·s)	167 ± 46†	169 ± 61†	148 ± 45	146 ± 47	142 ± 34†	133 ± 45†
T_I/T_{TOT}	0.40 ± .06†	0.39 ± .07	0.39 ± .07	0.38 ± .08	0.36 ± .07†	0.35 ± .06
$\dot{V}_L$ (L)	7.7 ± 2	7.6 ± 2	6.9 ± 1	6.5 ± 2	7.3 ± 2	6.6 ± 2
$\%\dot{V}_L$	0	0	16.4‡	20.5‡	44.8‡	44.6‡
f (breaths/min)	17 ± 3	16 ± 4	18 ± 5	16 ± 3	16 ± 4	16 ± 4
pH	7.41 ± .02	7.41 ± .03	7.42 ± .04	7.41 ± .03	7.42 ± .04	7.42 ± .03
P_{aCO_2} (mm Hg)	46 ± 9	47 ± 10	46 ± 9	46 ± 9	45 ± 8	45 ± 15
S_{aO_2} (%)	96 ± 1	96 ± 1	94 ± 2	94 ± 3	91 ± 8	92 ± 3

Values are mean ± SD, where applicable.
TTAV = transtracheal augmented ventilation (10 L/min)
MP = mouthpiece without transtracheal gas insufflation
LFTTO = low-flow transtracheal oxygen (3.4 ± 2 L/min)
PPTI = pleural pressure-time index
†TTAV was significantly different from MP ($p < 0.05$).
$\dot{V}_L$ = volume delivered to the lungs during inspiration
‡TTAV was significantly different from LFTTO ($p < 0.05$).
$\%\dot{V}_L$ = percent contribution to the volume delivered to the lungs during inspiration
f = respiratory rate
P_{aCO_2} = arterial partial pressure of carbon dioxide
S_{aO_2} = arterial oxygen saturation

post-Noc TTAV treadmill exercise study. In addition, patients were able to achieve a greater ($p < 0.005$) maximum heart rate during post-Noc TTAV exercise conditions (Figure 2C) and the rate of heart rate rise was less steep ($p < 0.05$) than in the pre-intervention study (Figure 3A). Furthermore, as shown in Figure 3B, the rate of pH decline was also less steep ($p < 0.05$) during the post-Noc TTAV exercise study.

Fiberoptic Bronchoscopy. Endoscopic inspection of the tracheobronchial mucosa (results not shown) did not find any important abnormalities, such as hemorrhage, exudates, ulceration, or necrosis, when patients were assessed under baseline conditions of LFTTO. Likewise, hemorrhage, exudates, ulceration, or necrosis were not seen after 3 months of Noc TTAV.

Individual Subject Response to Transtracheal Augmented Ventilation. As a group, subjects had statistically significant changes during TTAV with regards to inspired minute ventilatory requirements, WOB, and exercise capacity. Table 4 shows the data for each subject for inspired minute ventilation via the mouth, PPTI, and joules during exercise. In general, patients tended to respond in the direction of the group. Variations in magnitude of response were present.

Nocturnal Transtracheal Augmented Ventilation Administration and Monitoring during 3 Months of Treatment. Measured TTAV flow and F_{IO_2} in the home showed accurate delivery of the prescribed settings (10 L/min and 0.40 to 0.70, respectively). Technical difficulties were minor with the customized TTAV device and were limited to compressor repairs and adjustments of the servo humidifier settings. Patients reported good compliance and a nightly duration of TTAV use of 8 ± 2 hours. Nearly all patients reported improved sleep, and 11 of 13 patients related greater daytime activity with Noc TTAV.

Long-Term Nocturnal Transtracheal Augmented Ventilation Using an Oxygen Enricher (Second Series of Transtracheal Augmented Ventilation Patients)

Table 5 shows the clinical data. Ten women and 5 men (age 64.67 ± 6.65 yr) received Noc TTAV with the com-

Table 3. Ventilatory Drive Studies Obtained during MP Breathing Before and After 3-Month Trial of Nocturnal TTAV

	Before	After
Hypercarbia		
$P_{0.1}$ (cm H_2O)	7.3 ± 2.6	7.3 ± 2.6
$P_{ET}CO_2$ (mm Hg)	47.9 ± 2.6	45.0 ± 2.6
Hypoxemia		
$P_{0.1}$ (cm H_2O)	6.8 ± 2.6	6.4 ± 2.0
S_{pO_2} (%)	81.3 ± 4.5	83.6 ± 4.5

MP = mouthpiece breathing without transtracheal gas insufflation
Values are mean ± SD
TTAV = transtracheal augmented ventilation (10 L/min)
$P_{0.1}$ = airway occlusion pressure at the first 100 ms after airway closure
$P_{ET}CO_2$ = end-tidal carbon dioxide
S_{pO_2} = arterial oxygen saturation measured via pulse oxymetry

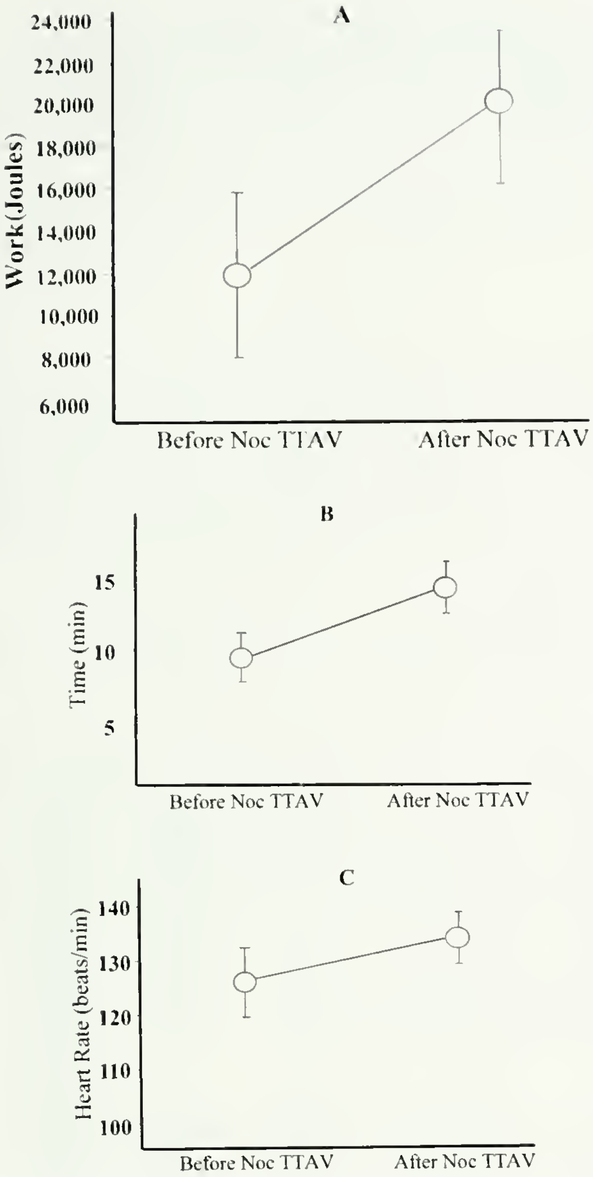

Fig. 2. Results of total work during exercise (graph A), exercise time (graph B), and heart rate at peak exercise (graph C) during graded treadmill exercise studies. Thirteen subjects breathed via mouthpiece (MP) without transtracheal flow during exercise. Studies were conducted before and after a 3-month trial of nocturnal transtracheal augmented ventilation (Noc TTAV). Results are expressed as mean ± 1 SEM. Total work was greater ($p < 0.05$) during the post-Noc TTAV condition. Likewise, duration of exercise was longer ($p < 0.005$) with post-Noc TTAV. Heart rate achieved at peak exercise was greater ($p < 0.005$) after 3 months of Noc TTAV.

mercially available oxygen enricher. Overall, patients had severe ventilatory impairment (forced expiratory volume in the first second = 0.82 ± 0.48 L) with P_{aCO_2} of 50.2 ± 5.93 mm Hg and normal pH (7.42 ± 0.03). Diagnoses included COPD (12), COPD and sleep apnea (1), interstitial lung disease (1), and restrictive pleural disease (1).

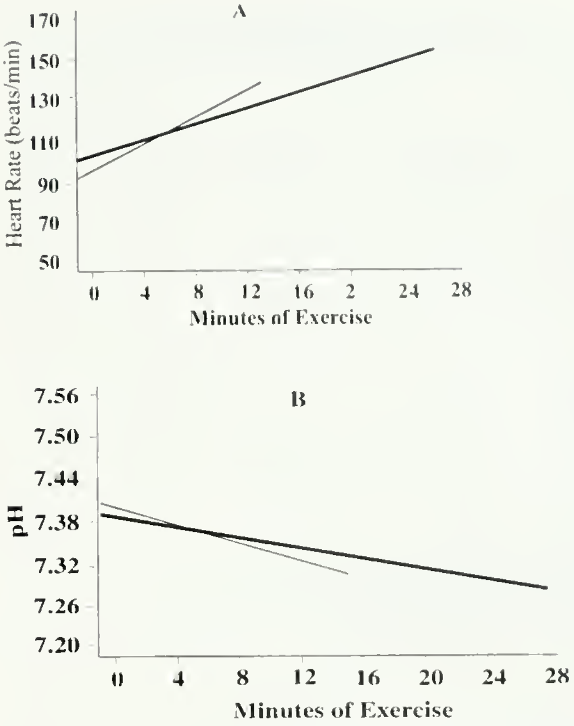

Fig. 3. Heart rate (graph A) and arterial pH (graph B) results during graded treadmill exercise studies. Thirteen subjects breathed via mouthpiece without transtracheal flow, during exercise. Studies were conducted before and after a 3-month trial of nocturnal transtracheal augmented ventilation (Noc TTAV). The thick lines denote the mean pre-Noc TTAV results. The thin lines denote the mean post-Noc TTAV data. Minutes of exercise are shown for the range of individual observations. The rate of rise in heart rate was less steep ($p < 0.05$) in the post-Noc TTAV condition. Furthermore, the rate of decrease of arterial pH was less steep ($p < 0.05$) in the post-Noc TTAV exercise study.

Prior to initiating regular LFTTO, patients had received home oxygen therapy via nasal cannula for 33.86 ± 21.78 months (range 0 to 85.15 mo). Subsequently, patients received standard LFTTO for 13.37 ± 27.19 months (range 0.33–105.23 mo) prior to starting Noc TTAV. Individuals received Noc TTAV for 28.69 ± 17.5 months, with a total of 430.32 patient-months of use (range 6.82–59.90 mo). The F_{IO_2} required with Noc TTAV was 47.73 ± 11.85%. Nocturnal oximetry found that S_{pO_2} was maintained above 90% during sleep. Patients tolerated Noc TTAV well, and there were no complications in this small series.

Technically, the oxygen enricher was adequate and less complex than the previously described custom device, but it was also less than ideal. Most patients required bleed-in of supplemental oxygen from their stationary source. Three patients died at home as a result of progressive worsening of COPD (Subjects 1, 3, and 12), and another patient died at home from an unrelated cardiac event (Subject 2). Seven patients died in the hospital: one expired from a massive pulmonary embolism following lung volume reduction sur-

Table 4. Individual Subject Response to TTAV

Subject	Inspired Minute Volume via Mouth (L)				Pleural Pressure-Time Index (cm·s)				Treadmill Exercise (J)	
	Before		After		Before		After			
	MP	TTAV	MP	TTAV	MP	TTAV	MP	TTAV	Before	After
1	11.8	7.77	10.18	6.99	187	130	143	110	41,348	43,704
2	9.78	5.83	7.94	3.44	179	150	141	85	809	542
3	8.46	4.25	6.55	3.95	247	207	244	177	7,054	16,278
4	6.27	2.92	5.82	1.75	130	147	131	119	40,204	44,182
5	10.02	3.85	7.12	3.58	168	129	183	155	5,657	12,900
6	9.02	2.25	9.88	5.05	153	118	236	189	426	821
7	7.64	4.34	8.01	2.94	165	145	148	75	15,756	26,021
8	7.28	2.54	7.5	5.35	242	172	153	140	741	1,681
9	6.46	3.6	9.98	1.69	149	104	304	120	4,940	20,941
10	8.67	5.79	9.03	5.55	133	161	156	131	10,951	46,036
11	9.06	7.94	11.33	8.71	200	184	173	219	1,698	13,288
12	7.34	3.68	5.77	2.3	138	105	111	142	3,294	11,510
13	4.45	2.11	3.7	2.04	78	89	72	63	22,987	29,804

Values are mean ± SD
TTAV = transtracheal augmented ventilation (10 L/min)
MP = mouthpiece breathing without transtracheal gas insufflation

Table 5. Nocturnal TTAV with an Oxygen Enricher: Long-Term Follow-Up

Subject	Diagnosis	Sex	Age (y)	FEV_1 (L)	FVC (L)	LFTTO (L/min)	P_{aCO_2} (mm Hg) (LFTTO)	pH (LFTTO)	F_{IO_2} (Noc TTAV)	Months on Noc TTAV	TTO Months Prior to Noc TTAV	NC Months Prior to TTO
1	COPD	F	62	0.90	2.00	3.0	50	7.42	35	44.52	24.37	24.33
2	COPD	M	64	0.78	2.04	4.0	50	7.40	32	6.82	2.80	85.15
3	COPD	F	60	0.45	0.91	3.0	50	7.44	57	18.62	1.03	36.50
4	COPD/OSA	M	63	2.37	3.01	3.0	50	7.44	60	57.77	1.00	54.93
5	COPD	M	70	0.81	2.07	3.0	45	7.42	59	31.51	1.43	45.50
6	COPD	F	76	0.61	1.41	1.0	41	7.39	55	11.51	1.07	45.50
7	COPD	F	62	1.02	2.36	2.0	46	7.41	37	23.61	0.47	27.83
8	COPD	M	74	0.70	1.81	4.0	45	7.44	66	24.69	26.63	36.50
9	ILD	F	54	0.86	0.88	5.0	61	7.50	54	9.34	105.23	48.66
10	COPD	M	60	0.58	1.42	4.0	45	7.45	53	59.90	1.00	33.50
11	COPD	F	68	0.39	1.13	1.5	54	7.39	35	14.82	23.27	0.73
12	COPD	F	74	0.97	1.75	1.0	50	7.38	38	29.80	0.33	8.00
13	COPD	F	62	0.45	1.29	4.0	62	7.37	47	21.21	1.00	29.83
14	RPD	F	55	0.94	0.95	1.0	56	7.41	31	50.82	9.77	0.00
15	COPD	F	66	0.42	1.42	2.0	48	7.43	57	25.38	1.10	30.90
Mean			64.67	0.82	1.63	2.77	50.20	7.42	47.73	28.69	13.37	33.86
SD			6.65	0.48	0.60	1.29	5.93	0.03	11.85	17.15	27.19	21.78

TTAV = transtracheal augmented ventilation (10 L/min)
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
LFTTO = low-flow transtracheal oxygen
P_{aCO_2} = arterial partial pressure of carbon dioxide
F_{IO_2} = fraction of inspired oxygen
TTO = transtracheal oxygen
NC = nasal cannula
COPD = chronic obstructive pulmonary disease
OSA = obstructive sleep apnea
ILD = interstitial lung disease
RPD = restrictive pleural disease

gery (Subject 11); another succumbed to massive gastrointestinal bleeding following admission for a tibia/fibula fracture (Subject 13); and another expired from pneumonia complicating hip surgery (Subject 15). An additional individual (Subject 6) moved out of state to reside with her daughter, where TTAV was unavailable. Three patients continue to use Noc TTAV (168.49 patient-months follow-up).

Discussion

This is a preliminary observational study in a small number of patients, with no untreated or conventional control group. Each patient served as his or her own control. This type of observational study was used in the very first study of long-term oxygen therapy.[20] Previous studies have demonstrated the benefit of transtracheal flows from 0 to up to 15 L/min in the treatment of obstructive sleep apnea.[21–25] However, this is the first in-depth evaluation of a new method for nocturnal transtracheal augmentation of ventilation for patients with severe respiratory disease. Our preliminary results demonstrate that Noc TTAV is well tolerated in the treatment of stable outpatients with chronic hypoxemia and severe respiratory disease. The transtracheal insufflation of 10 L/min of oxygen-enriched humidified gas decreased PPTI. This reduction in the oxygen cost of breathing was accompanied by decreased V_T inspired through the upper airway and shortened T_I, without significant alterations in respiratory frequency. Increase in transtracheal insufflation was counter-balanced by further decrease in the volume inspired via the upper airway, but the total gas delivered to the lung during inspiration remained relatively constant. Transtracheal gas flow did not alter P_{aCO_2}.

This investigation evaluated the effect of tracheal insufflation at higher flows than used in previous studies.[3–11] It is also the first study to show that a number of physiologic changes related to increased transtracheal gas flow persist over time.

P_{aCO_2} was not significantly different when the MP control subjects were compared to either LFTTO or TTAV subjects, in spite of the fact that transtracheal gas delivery was shown to significantly augment ventilation (16–21% with LFTTO and 45% with TTAV). Also, P_{aCO_2} was unchanged when post-Noc TTAV data for MP, LFTTO, and TTAV were compared to the pre-intervention data. Thus, it appears that subjects maintained a relatively constant $\dot{V}_L$ and P_{aCO_2} and benefited from a reduction in the work involved in generating the tidal breath. Perhaps P_{aCO_2} did not change in the subjects in this investigation because they were medically stable and had only mild to moderate hypercapnia. Unstable or more severely hypercapnic patients might experience reduced P_{aCO_2} with TTAV.[13] In addition, ventilatory drive was unchanged when the post-Noc TTAV results were compared to the baseline evaluation done following long-term treatment with standard LFTTO.

An interesting finding in this study is that exercise capacity was greater following a 3-month trial of Noc TTAV than at baseline, where patients had only been receiving LFTTO. Exercise time, total work, and heart rate at peak exercise were significantly increased in the post-intervention testing. A reduction in the slope of the rise in heart rate was observed with exercise. Also, the decrease in pH was less steep following the Noc TTAV trial.

The mechanism for improved exercise capacity following Noc TTAV is not clear. There were no other changes in the general care of the patients. A carry-over effect from previous therapy with LFTTO or the passage of time is unlikely, as patients had previously had adequate opportunity (29 ± 26 mo) to plateau from benefits of LFTTO therapy. Patient familiarization with the exercise protocol could have contributed to improved performance on the post-exercise test. However, the improvements were rather marked and the second exercise study was done 3 months following the first. These physiologic improvements in heart rate and ABG values suggest that it is unlikely that changes in exercise capacity were due to a placebo. Perhaps a degree of nocturnal rest of the respiratory muscles during TTAV resulted in improved muscle strength.

Noc TTAV was well-tolerated. Nocturnal polysomnography studies showed that sleep efficiency with the high flows used with Noc TTAV was not significantly different than the sleep efficiency seen with the control condition of LFTTO. Likewise, sleep efficiency with Noc TTAV did not significantly deteriorate over time. Patients reported excellent compliance with the technology, but timers to objectively record operating hours of the equipment were not incorporated in this study design.

During both the 3-month trial and the more long-term follow-up with the oxygen enricher, Noc TTAV was demonstrated to be safe. Fiberoptic bronchoscopic examination following 3 months of Noc TTAV did not find important mucosal abnormalities such as hemorrhage, exudates, ulceration, or necrosis. Furthermore, oxygen saturation during sleep was adequate. Technical difficulties were minor and were more common with the customized device than with the subsequent long-term use of a commercial product. No complications were encountered with either the 3-month Noc TTAV intervention or the long-term evaluation of a second group of 15 patients. Experience with Noc TTAV using the commercial oxygen enricher was substantial, with a mean of 28.69 months of follow-up and a cumulative total of 430.32 patient-months. During the 3-month evaluation, one patient was taken off Noc TTAV because of increased anxiety associated with rigorous testing and the new technology. As with LFTTO,[3] the presence of disabling anxiety should probably constitute a relative contraindication for Noc TTAV.

The purpose of this report is simply to describe our initial experience with TTAV. Patients with chronic severe respiratory insufficiency from more than one etiology were evaluated. This heterogeneity of diagnoses was also present in initial reports on LFTTO therapy[2–4,8] and earlier physiologic studies.[10,11] However, COPD was the most common disease in the present report (69% in the 3-month study and 87% in the long-term evaluation). Though not addressed in the present investigation, there may be subtle variations in response to TTAV based on diagnosis. Patients enrolled in the study had mature transtracheal tracts and were on TTO for a relatively long period (29 ± 26 mo). They probably tolerated the high flows with Noc TTAV because their airways were accustomed to transtracheal gas delivery. Transtracheal oxygen was not initiated because of refractory hypoxemia, and patients were not end-stage. In fact, their entry data were similar to a large series of patients beginning transtracheal oxygen therapy.[3] By previous selection criteria, they were relatively active and were competent in self-care of their catheter systems.[3]

Potential advantages to this method of augmented ventilation include enhanced compliance and comfort, as well as improved exercise capacity. Though TTAV may be of benefit to some individuals with severe, chronic hypercapnia or to individuals in the process of weaning from mechanical ventilation,[26] the results of this study show improvement in patients with mild to moderate hypercapnia. Since patients with chronic severe lung disease often need continuous supplemental oxygen in addition to nocturnal augmentation of ventilation, the administration of daytime LFTTO and Noc TTAV appears to have some potential advantages over daytime nasal oxygen and nocturnal bilevel positive airway pressure.[27,28]

Transtracheal augmentation of ventilation is yet another method of administering high gas flows via the tracheobronchial tree. This method of ventilation should be distinguished clinically from either constant flow ventilation or tracheal gas insufflation (TGI). Constant flow ventilation delivers very high flows of gas via right and left bronchial catheters to achieve ventilation, and it sustained life in a paralyzed animal model.[29,30] TGI involves administration of tracheal gas flow during concurrent use of mechanical ventilation in the management of hypercapnia associated with severe oxygenation failure.[31,32] In contrast to constant flow ventilation, subjects receiving TTAV breathe spontaneously and ventilatory support is achieved with lower flows and without the need for bilateral bronchial catheterization. TTAV is different than TGI in that other methods of mechanical ventilation are not used simultaneously. Furthermore, TTAV is administered via an open system rather than the closed system used when TGI is delivered via a cuffed endotracheal tube.

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An Evaluation of Automode, a Computer-Controlled Ventilator Mode, with the Siemens Servo 300A Ventilator, Using a Porcine Model

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BACKGROUND: Weaning of mechanical ventilation in patients optimally includes meeting their needs by making frequent ventilator adjustments. The Siemens Servo 300A mechanical ventilator is designed to allow the ventilator to be interactive with the patient's needs by making breath-by-breath adjustments in both control and support modes. We undertook the following experiment to validate that the Automode algorithm responded appropriately using a pediatric animal model when apnea occurred and if there was any impact on work of breathing. METHODS: We ventilated 6 sedated spontaneously-breathing piglets using Automode in pressure-regulated volume control/volume support (PRVC/VS) mode, pressure control/pressure support (PC/PS) mode, and volume control/volume support (VC/VS) mode. Data were collected using both a computerized respiratory monitor and data acquisition system that recorded and analyzed individual animal breaths for response time, effort of triggering, and work of breathing. Data collection began with the animals breathing spontaneously in each support mode, followed by the administration of a short-acting neuromuscular blocker (succinylcholine) to induce apnea, thus allowing the ventilator to switch between modes automatically. Data collection was continued before, during, and after apnea to observe the duration of inspiratory effort, trigger response time, and any significant pressure or flow variances of the Automode feature. In addition, patient work of breathing (WOB_P) and ventilator work of breathing (WOB_V) were measured before and after each phase. RESULTS: We found no instances of failure of Automode to follow the predetermined algorithms. There was a difference in both the amount of change in pressure and most negative deflection of pressure by each animal during triggering in the post-paralysis phase ($p < 0.05$). Response time for individual breaths was shorter from initiation of breath to most negative deflection of pressure during the post-paralysis phase ($p < 0.05$). Maximum flow reached was lower in the post-paralysis phase for VC/VS and PC/PS ($p < 0.05$). We also found WOB_P decreased and WOB_V increased in the post-paralysis phase for all modes tested. CONCLUSIONS: The Automode algorithm performed as expected in this animal experiment. We conclude that differences in response time and negative deflection of pressure, as an indication of animal effort, and maximum flow reached were due to continued weakness from the neuro-muscular blocker. However, the ventilator continued to trigger despite decreased effort by the animal. [Respir Care 2001;46(1):26–36] *Key words: artificial ventilation equipment, positive-pressure respiration, inspiratory work, artificial respiration, positive end-expiratory pressure, Automode.*

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Introduction

Weaning patients from mechanical ventilators continues to be one of the most perplexing yet vital issues in caring for critically ill infants and children. Reversing the disease process that committed the patient to mechanical ventilation and then successfully decreasing ventilator support to a level that allows for extubation are the primary goals of weaning. There are various opinions about the proper way to wean patients from mechanical ventilation.[1-3] However, delays in weaning patients from mechanical ventilator support are associated with a combination of equipment factors, patient conditions, and caregiver decisions regarding weaning and extubation criteria.

Equipment factors relate to the ability of the mechanical ventilator to meet the needs of the patient. These equipment factors have an increased importance in pediatric patients, in which work of breathing (WOB) associated with the equipment is increased.[4-7] We believe that in order to wean patients optimally and ensure patient comfort, ventilator adjustments would have to be made moment-to-moment in response to the patient's immediate physiologic needs. It is, of course, unrealistic for any medical, nursing, or respiratory care staff to perform in this manner. In response to this need for improved patient-ventilator interaction, some researchers have attempted to create an interactive computer-directed weaning system, with promising results.[8-11]

In order to enhance weaning of patients from mechanical ventilation, the Servo 300A (Siemens Medical Systems, Danvers, Massachusetts) mechanical ventilator with Automode seeks to be more interactive with the patient. Automode is a patient-interactive mode that uses a computer-directed algorithm to direct both control and support modes, depending on the patient's needs. When Automode is enabled, it allows the ventilator to switch between volume control/volume support (VC/VS), pressure control/pressure support (PC/PS), and pressure-regulated volume control/volume support (PRVC/VS) modes with spontaneously triggered breaths. When Automode is activated, the ventilator switches to the corresponding support mode after the patient triggers 2 consecutive breaths. The ventilator remains in the support mode as long as the patient continues to breathe spontaneously. If the patient stops triggering, the ventilator automatically switches back to the clinician-selected control mode.

This study was designed to evaluate the ability of the computerized algorithm incorporated within the Servo 300A ventilator to respond to drug-induced apnea by switching between control and support modes, using a pediatric animal model. Patient WOB and response time of the ventilator were measured as indicators of the impact on the patient's ability to wean effectively from mechanical ventilation.

Methods

Animal Model

The Animal Review Committee of the University of Arkansas for Medical Sciences approved this study. Animals were cared for in accordance with the standards for care and use of laboratory animals set forth by the university.

Animal Model Preparation

Studies were performed on 6 pigs on different days. The animals were 2–3 weeks old and weighed approximately 6–10 kg each. This animal model was selected because respiratory rate, tidal volume (V_T), and minute ventilation are comparable to those of pediatric patients. Twenty-four to 48 hours prior to the study day, vascular catheters (5 French) were surgically placed via cutdown in the external jugular vein for drug administration. On the study day, all animals were intravenously anesthetized with midazolam (0.25 mg/kg) and propofol (3 mg/kg) and intubated with a 4.0–4.5 mm-inner-diameter cuffed endotracheal tube. Endotracheal tube location was confirmed by direct visualization and the cuff inflated to a minimal occlusion pressure. After intubation, the animal was placed into a prone position in a temperature-controlled chamber. Gas humidification was maintained by a heat and moisture exchanger (Humidivent 600, Portex, Keene, New Hampshire) positioned on the endotracheal tube between the animal and the pneumotachograph (Fig. 1).

Supplemental intravenous anesthesia was administered continuously via the external jugular venous catheter. The anesthesia consisted of midazolam (0.15 mg/kg/h) and propofol (10 mg/kg/h). The animal's heart rate, respiratory frequency, pulse oximetry saturation, and temperature were monitored continuously with a physiologic monitor. The level of sedation was clinically monitored in order to maintain the animal in a light sleep, breathing spontaneously, arousable with interventions or stimulation, but returning to sleep.

Conducting the Automode experiment required the animals to become apneic during each study setting, thus allowing the ventilator to switch modes automatically. Succinylcholine, a short-acting neuromuscular blocking agent, was used to temporarily paralyze the animals (2 mg/kg). Since each animal responded differently to the succinylcholine, dosages of the medication were adjusted to induce the necessary time of apnea for each animal. The apnea period varied among the animals: each animal was apneic for at least 30 seconds but not longer than 4 minutes.

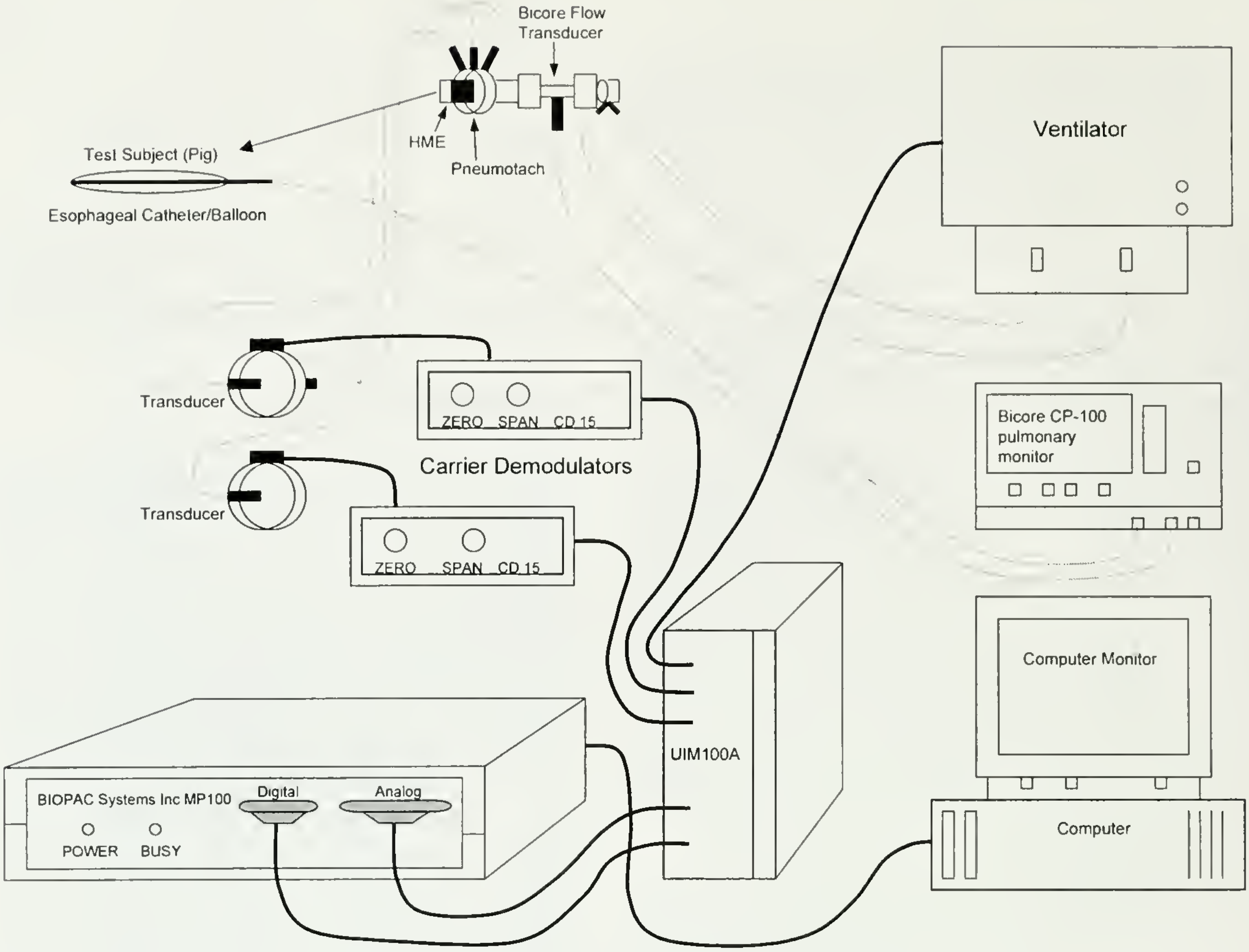

Fig. 1. Study setup components include Biopac MP-100 system (including UIM 100A component that links analog and digital inputs and outputs), Bicore monitor, Bicore flow transducer, ventilator, computer, computer monitor, heat and moisture exchanger (HME), pneumotachograph (Pneumotach), transducers, carrier demodulators, and an esophageal catheter/balloon. Dotted lines represent tubes. Solid lines represent cables.

Before performing the next experiment, a rest period was allowed for the animal to fully recover from the succinylcholine. We considered the animal fully recovered from the succinylcholine when it had returned to its normal baseline state (respiratory rate, pulse oximetry, V_T).

Equipment Setup

The animals were sedated, intubated, and placed on the Servo 300A ventilator in the specific mode and settings, according to the study protocol. Each animal was studied on 2 separate days, using PC/PS, PRVC/VS, and VC/VS modes in random order. In the pressure-controlled modes, a peak inspiratory pressure (PIP) adequate to deliver 6 mL/kg V_T and pressure support of 5 cm H_2O was used. In the volume-controlled modes, a V_T of 6 mL/kg was used. In all modes, ventilator frequency was 10 breaths/minute, positive end-expiratory pressure (PEEP) was 5 cm H_2O, inspiratory rise time was 5%, and the fraction of inspired oxygen (F_{IO_2}) was 0.30. All studies were conducted in the pediatric patient range, using flow-triggering, with the sensitivity set in the middle of the "green zone" on the Servo 300A. When the pointer of the sensitivity dial rests in the green zone, a ventilator breath is initiated when the patient's effort causes a brief drop in flow, of 0.3–1 L/min.[12] Flow is sensed at the expiratory flow transducer. The trigger sensitivity is determined as the difference between inspiratory flow and expiratory flow.

Each animal was studied on 2 separate days, in all modes in which Automode could be activated. For all experiments, data were collected for at least 5 spontaneous triggered support mode breaths. Succinylcholine was then administered to induce temporary apnea. Data collection continued uninterrupted as the ventilator switched to the

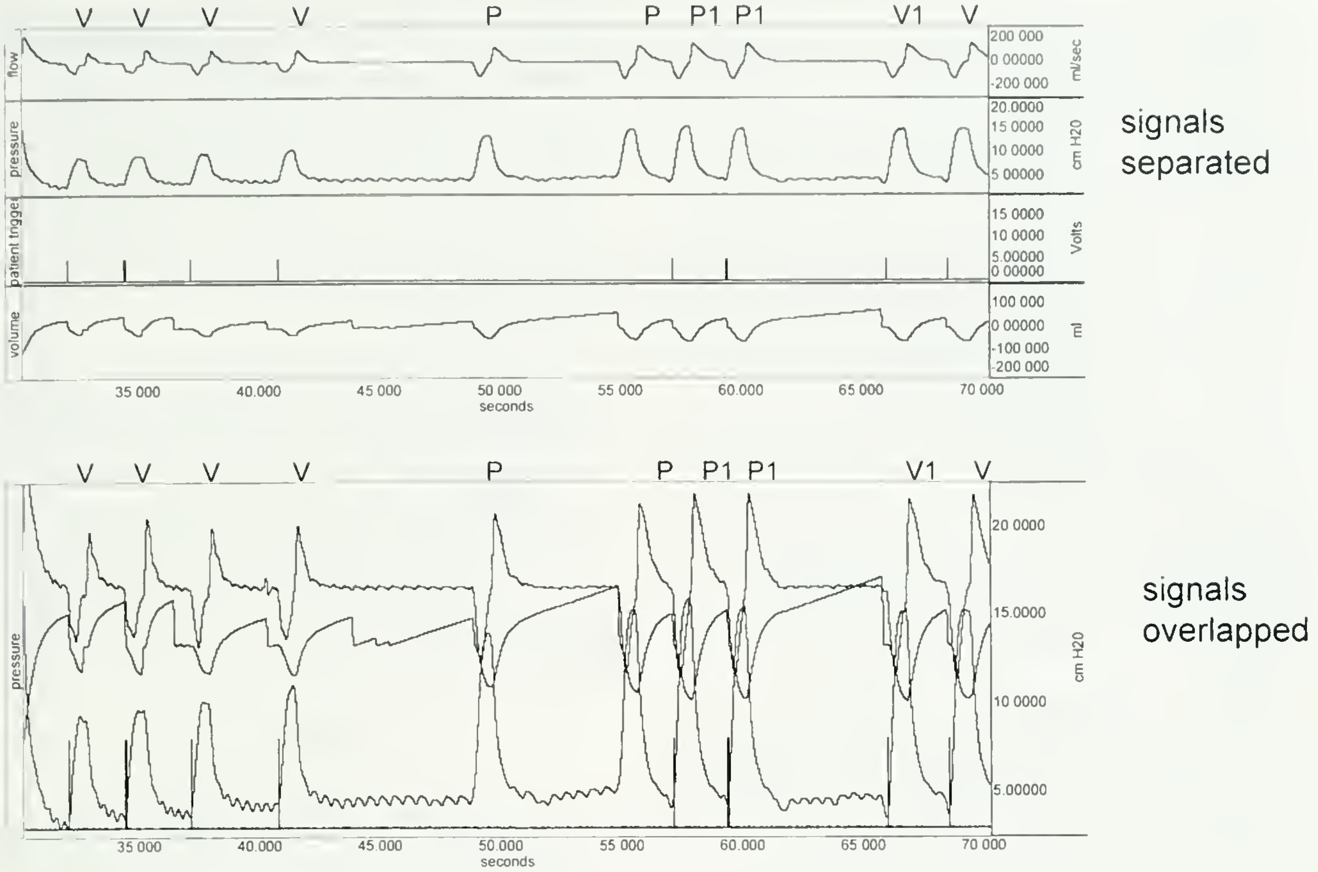

Fig. 2. Graph of data collected during pressure-regulated volume control/volume support (PRVC/VS) mode, with positive end-expiratory pressure (PEEP) 5 mm Hg, flow triggering, respiratory rate 10, pediatric range. This figure shows the switch from VS to PRVC and back to VS. Breaths marked "P" are PRVC breaths. Breaths marked P1 are patient-triggered PRVC breaths. Breaths marked V are VS breaths. V1 is a VS breath at the previous PRVC level. The top graph shows all signals separated for scales. The bottom graph shows the same set of breaths with the pressure scale and all signals overlapped. Pressure waveforms were measured at the airway.

control mode and back to the support mode as the animal began to breathe spontaneously again (Fig. 2). Only data from the pre-paralysis and post-paralysis phases were reported, since only ventilator work was obtained while the animal was apneic.

Data Acquisition

Airway pressure and flow rates were measured at the proximal end of the endotracheal tube, using a differential flow transducer equipped with a pneumotachograph/pressure transducer system connected to the BiCore CP-100 monitor (BiCore Monitoring Systems, Irvine, California). The dead space within the flow transducer was 11 mL. Intrapleural pressure was inferred using a standard commercially manufactured esophageal catheter also connected to the BiCore CP-100 pulmonary monitor. Esophageal balloon placement was confirmed using the occlusion test.[13]

The BiCore monitor records both measured and calculated respiratory parameters. The measured parameters were airway pressure, esophageal pressure, and airway flow.[14] Patient WOB (WOB_P) and ventilator work (WOB_V) are calculated from these measurements. WOB_P is the amount of work done by the respiratory muscles to move a given volume of gas during spontaneous breathing or in a ventilator-assisted breath.[15] The BiCore CP-100 monitor calculates WOB_P by integrating the area of the esophageal pressure and V_T loop from the start of inspiration until either the end of inspiration or until esophageal pressure becomes greater than end-expiratory esophageal pressure.[16] WOB_V is the physical force required by the ventilator to move a given volume of gas into the lung with a relaxed chest wall.[15] WOB_V is calculated in the BiCore CP-100 monitor by integrating the area of the airway pressure-volume loop.[16] The chest wall compliance was directly measured by paralyzing each animal with succinylcholine (2 mg/kg), ensuring an adequate respiratory rate and V_T with a control mode of mechanical ventilation. While the animal was in a relaxed state, chest wall compliance was obtained by analysis of the esophageal pressure and V_T

loop, using the Campbell-diagram software, and was integrated into the calculation of WOB.[17] In addition to WOB, the BiCore also calculates respiratory drive ($P_{0.1}$) and inspiratory time fraction (ratio of inspiratory time to total breathing-cycle time or T_I/T_{TOT}). Diaphragmatic contraction is a response to stimulation from the neural drive and $P_{0.1}$ is a measure of this force in cm H_2O. It is defined as the airway occlusion pressure at the first 100 ms after airway closure, prior to the animal's conscious recognition of occlusion.[18] This value represents work expenditure during the animal's initiated ventilator breath and if elevated represents an increase in work by the animal. Consequently, a low $P_{0.1}$ value may indicate when respiratory drive is blunted—for example, when there is residual effect from the neuromuscular blocking agent. Concurrently, T_I/T_{TOT} is a measure of endurance and is defined as the ratio of the inspiratory time to the total time of the respiratory cycle. This value is a ratio and therefore there has no unit of measure. If respiratory muscles fatigue, more time is spent in inspiration, so T_I/T_{TOT} decreases.[16] Theoretically, this may also occur with the effects of neuromuscular blocking agents.

Additional measurements of respiratory flow and pressure waveforms were acquired using the Biopac MP-100 System (MP-100 with AcqKnowledge software, Biopac Systems, Santa Barbara, California), a computer-based data acquisition system that performs many of the same functions as a chart recorder. For each Biopac MP-100 System study, a nonheated 0–35 L/min pneumotachograph was placed in line between the animal and ventilator. Respiratory flow was obtained by connecting 2 pressure taps on the differential flow pneumotachograph (Model 4500A, Hans Rudolph, Kansas City, Missouri) to a variable-reluctance pressure transducer (± 2 cm H_2O) and carrier demodulator (CD15, Validyne Engineering, Sacramento, California). To monitor pressure, the pneumotachograph was equipped with a pressure hose, barb-type port that allowed airway pressure sampling. This port was connected to a separate variable-reluctance pressure transducer (± 50 cm H_2O) (MP45–871, Validyne Engineering, Sacramento, California) and carrier demodulator. All output signals were routed via an analog channel box into the Biopac MP-100 data acquisition unit, converting them into digital signals that can be processed with a computer. Signals were obtained at a rate of 1,000 samples per second. Volume measurements were obtained through the computer by integrating the flow signal. In addition, a patient trigger voltage signal was routed via a custom-made cable to the analog channel box and MP-100 and displayed by the computer, utilizing Biopac's AcqKnowledge software. Calibrations were tested using 2 known high and low signals.

These data were used to compare breath-by-breath respiratory patterns of our animal model. Time measurements were taken from the initiation of a breath (start of deflection of inspiratory flow) to the most negative deflection of pressure and from the initiation of the breath to the maximum flow obtained during the breath cycle (Figs. 3 and 4). We defined these measurements as duration of inspiratory effort. Other data obtained were most negative deflection of pressure at the airway, maximum flow, and the change in pressure from the start of deflection of pressure to the most negative deflection in pressure (ΔP).

Statistical Analysis

Each animal was used as its own control. Descriptive statistics were performed for WOB_P, WOB_V, respiratory rate, minute ventilation, peak inspiratory flow, peak expiratory flow, PIP, $P_{0.1}$, T_I/T_{TOT}, duration of inspiratory effort, maximum flow, and ΔP. The mean values for these were compared by the Wilcoxon signed rank test for significant differences, using commercially available statistical software, SPSS for Windows (SPSS, Chicago, Illinois). A p value ≤ 0.05 was considered statistically significant.

Results

Table 1 lists mean values for measurements obtained from respiratory wave forms collected with the Biopac MP-100 system. The most negative deflection of pressure needed to generate a breath was lower in the pre-paralysis phase of the experiment, by a mean of 79% across all modes, which was statistically significant. Also, in all modes, the duration of inspiratory effort (elapsed time from initiation of breath to most negative deflection of pressure), was shorter (30–42%) in the post-paralysis phase, whereas the time from initiation of breath to maximum flow in the post-paralysis phase was slightly longer for PRVC/VS (17%) than for VC/VS (3%) or PC/PS (< 1%). These differences were not statistically significant and indicate that there was little change in inspiratory flow delivery to the animals in the VC/VS and PC/PS ventilation modes. However, during the post-paralysis phase, there was a significant decrease in the maximum flow reached in VC/VS (45%) and PC/PS (62%). In the post-paralysis phase of the experiment PRVC/VS also showed a decrease (24%) in maximum flow, but this difference was not statistically significant.

Figure 2 shows signals for pressure, flow, volume, and patient trigger for the pre-paralysis and post-paralysis phases. When the animal switched from PRVC to VS, the next 2 animal-initiated breaths were PRVC breaths. The next triggered breath was delivered as a PRVC breath. The next breath was a VS breath delivered with a pressure level equal to the last PRVC breath. There were no episodes of arterial oxygen desaturation during the switch from control to support modes.

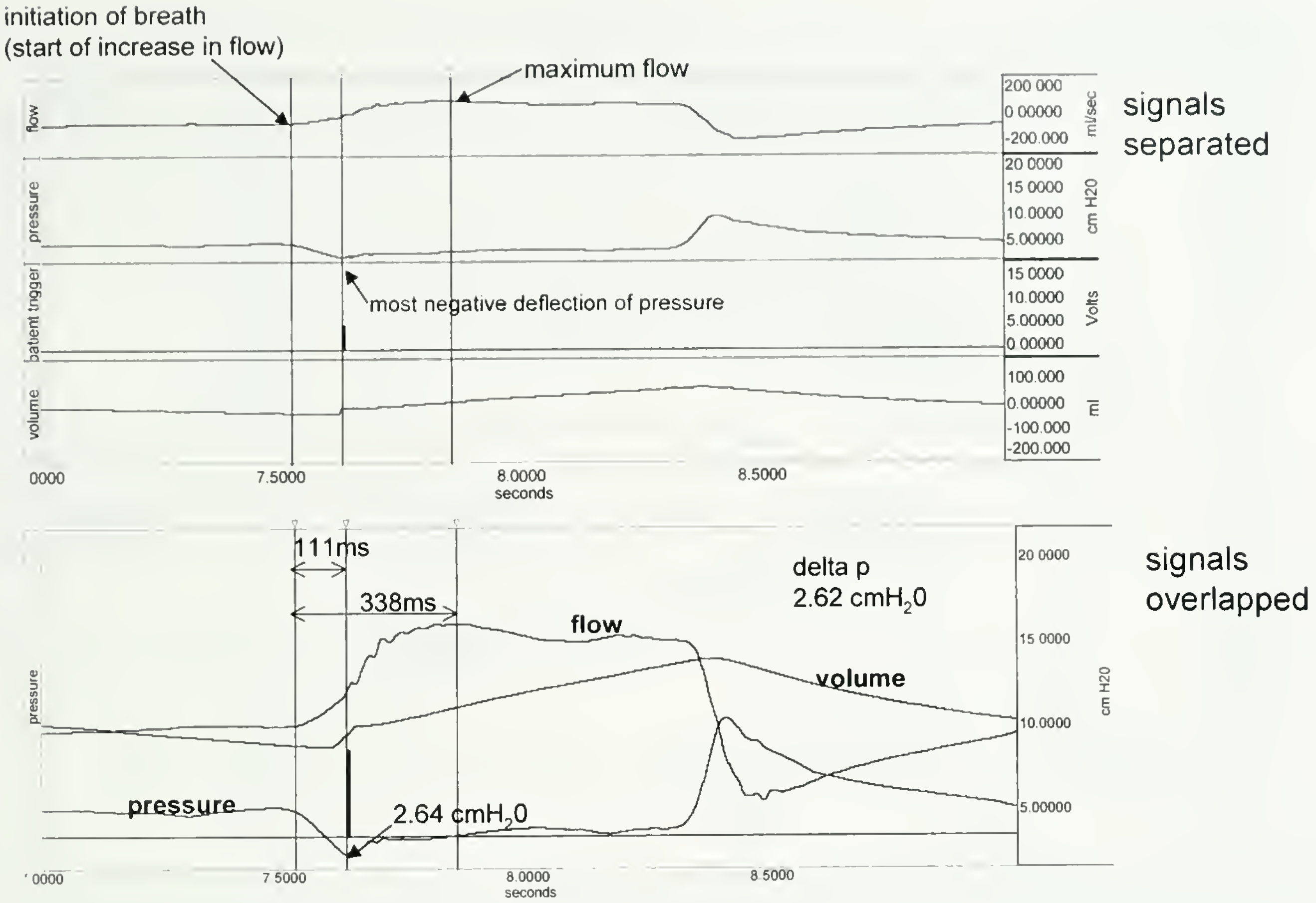

Fig. 3. Graph of data collected during volume control/volume support (VC/VS) mode, with positive end-expiratory pressure 5 mm Hg, respiratory rate 10, flow triggering, pediatric range. This figure shows a single pre-paralysis breath. The top graph shows all signals separated for scales. The bottom graph shows the same breath with the pressure scale and all signals overlapped. Pressure waveforms were measured at the airway. Delta p (the change in pressure from the start of deflection of pressure to the most negative deflection in pressure) = 2.62 cm H_2O.

The magnitude of negative deflection of pressure represents the difference between the baseline pressure and the most negative deflection of pressure (ΔP), which is a representation of the magnitude of the animal's effort. The ΔP decreased significantly (146–248%) in the post-paralysis phase for all modes studied. For example, in PRVC/VS the animal created a ΔP of 4.22 cm H_2O in the pre-paralysis phase, but only exerted a ΔP of 1.28 cm H_2O in the post-paralysis phase (see Figs. 3 and 4).

Figure 5 is a box plot of WOB_P before and after paralysis for each mode. In all ventilator modes, the WOB_P was an average of 150% lower in the post-paralysis phase ($p = 0.028$).

Table 2 lists mean values for data collected from the BiCore CP-100 monitor. WOB_V increased by an average of 55% in the post-paralysis phase, representing increased work by the ventilator, thus more support. Respiratory rate (8–24%) and minute ventilation (19–42%) were lower in the post-paralysis phase for all 3 modes. Peak inspiratory flow (9–27%) was higher and peak expiratory flow was on average 10% lower in the post-paralysis phase. PIP (2–11%) showed minimal differences between pre-paralysis and post-paralysis across all modes. For all the values above, none of the differences in the values were considered clinically important except WOB_V.

The $P_{0.1}$ and T_I/T_{TOT} values were also collected by the BiCore monitor and are included in Table 2. Both of these measurements may reflect residual effects of the neuromuscular blocking agent. However, in this experiment the pre-paralysis and post-paralysis values were not increased to a level of clinical importance.

Discussion

Although devices implementing the concepts that Automode is based on have been anticipated in the patient care arena, validation of this feature on the Servo 300A in the animal lab is essential to assure patient safety. The data

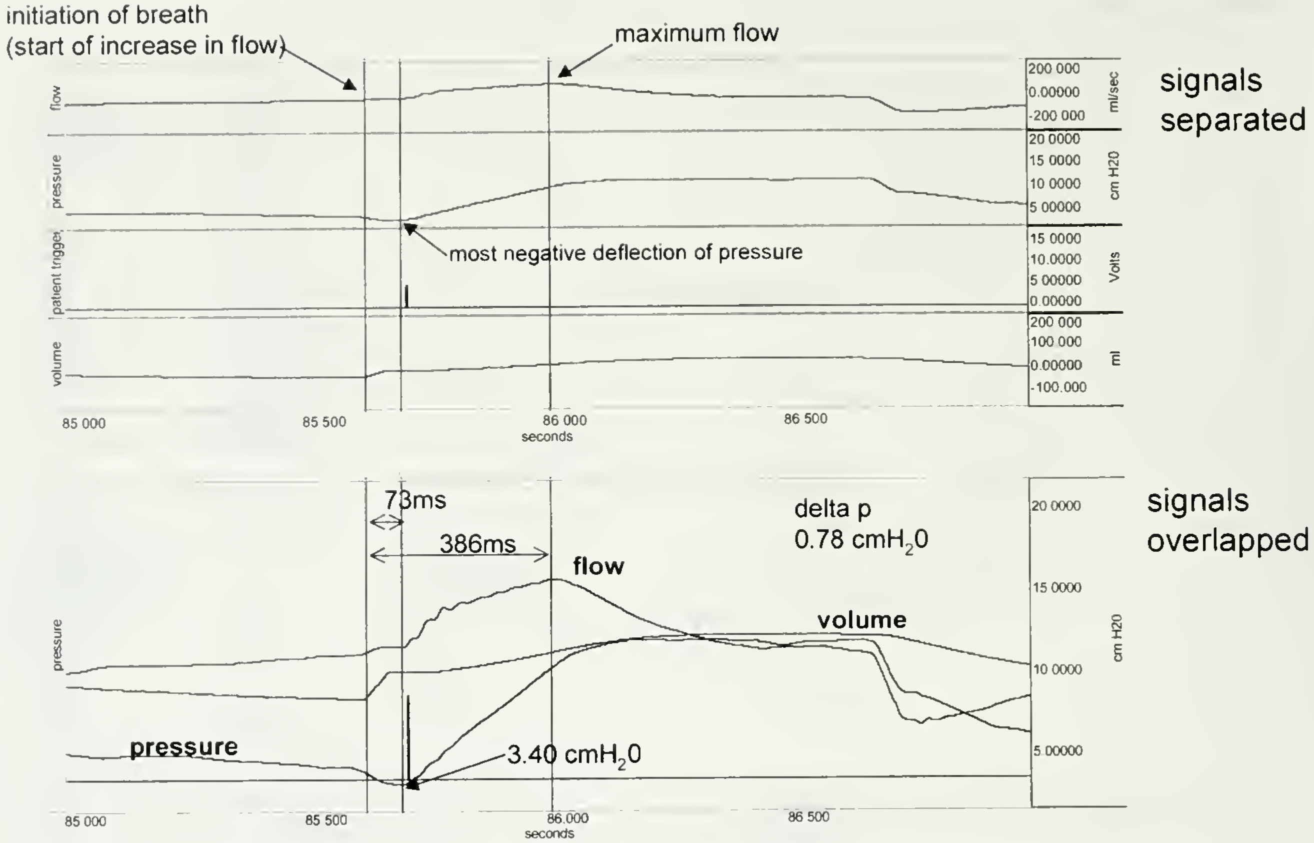

Fig. 4. Graph of data collected during volume control/volume support (VC/VS) mode, with positive end-expiratory pressure 5 mm Hg, respiratory rate 10, flow triggering, pediatric range. This figure shows a single post-paralysis breath (same animal and study as Figure 3). The top graph shows all signals separated for scales. The bottom graph shows the same breath with the pressure scale and all signals overlapped. Pressure waveforms were measured at the airway. Delta p (the change in pressure from the start of deflection of pressure to the most negative deflection in pressure) = 0.78 cm H_2O.

obtained during this experiment indicated that the Automode algorithm performed as expected, without causing an increase in WOB or ventilator response time.

Weaning patients from mechanical ventilation requires waiting until the disease process that caused the patient to need assisted ventilation reverses and then successfully decreasing ventilator support to a level that allows extubation. Successfully weaning patients off the ventilator rapidly is of utmost importance because of inherent risks involved in such an invasive medical intervention.[19] Restoring infants and children to a physiologic state of normal spontaneous ventilation is critical to their long-term prognosis because of the special risks they face due to their anatomic and physiologic differences from adults.[20]

An important factor in successful weaning of mechanical ventilation is the clinician's ability to manipulate the ventilator so that it responds to the patient's physiologic respiratory demands by providing more or less support, as needed. If the ventilator itself could make these adjustments, based on the patient's physiologic needs and ventilatory pattern, it would provide optimal weaning.[21] Experiments with the concept of closed-loop ventilation have been investigated by other researchers attempting to interface patients and ventilators, using computer-directed algorithms in this way.[8-10]

The person making the decision to wean the patient may have an impact on the length of mechanical ventilation. Respiratory therapist-driven weaning protocols are being examined as an alternative to current standard practices of weaning.[22,23] It is thought by some health care providers that respiratory therapists might be optimal weaning facilitators. Decision-making by respiratory therapists has been thought to have the potential to reduce the length of mechanical ventilation, because of the availability of respiratory therapists at the bedside during their frequent patient assessments. Respiratory therapists frequently perform diagnostic functions such as sampling for arterial blood gas analysis, pulse oximetry, end-tidal carbon dioxide measurement, and airway function screening, and they have the expertise to interpret that information.

Table 1 Mean Values from Measurements of Respiratory Wave Forms

Measurement	Pre-Paralysis	Post Paralysis	p Value
Pressure Regulated Volume Control/Volume Support (Ventilator Setting) (PRVC/VS)			
Most negative deflection of pressure (cm H_2O)	1.87 ± 0.99	3.80 ± 0.47	0.028
Initiation of breath to most negative deflection in pressure—time elapsed (ms)	132 ± 69	101 ± 67	0.028
Maximum flow (mL/s)	198 ± 43	160 ± 33	0.173 (NS)
Initiation of breath to maximum flow—time elapsed (ms)	310 ± 144	361 ± 111	0.463 (NS)
Change in pressure from initiation of breath to most negative pressure (cm H_2O)	4.22 ± 1.20	1.28 ± 0.52	0.028
Volume Control/Volume Support (Ventilator Setting) (VC/VS)			
Most negative deflection of pressure (cm H_2O)	2.37 ± 0.23	4.20 ± 0.69	0.043
Initiation of breath to most negative deflection in pressure—time elapsed (ms)	115 ± 25	82 ± 18	0.043
Maximum flow (mL/s)	184 ± 37	127 ± 12	0.043
Initiation of breath to maximum flow—time elapsed (ms)	370 ± 121	379 ± 51	0.893 (NS)
Change in pressure from initiation of breath to most negative pressure (cm H_2O)	3.80 ± 1.04	1.09 ± 0.51	0.043
Pressure Control/Pressure Support (Ventilator Setting) (PC/PS)			
Most negative deflection of pressure (cm H_2O)	2.54 ± 0.79	4.01 ± 0.30	0.028
Initiation of breath to most negative deflection in pressure—time elapsed (ms)	154 ± 75	108 ± 43	0.028
Maximum flow (mL/s)	199 ± 47	123 ± 25	0.028
Initiation of breath to maximum flow—time elapsed (ms)	402 ± 72	405 ± 102	0.917 (NS)
Change in pressure from initiation of breatb to most negative pressure (cm H_2O)	3.06 ± 1.07	1.24 ± 0.31	0.028

Values are mean ± standard deviation.
NS = not significant

However, there are currently no data documenting the use of that type of weaning protocol with neonatal and pediatric patients.

Automode may be a useful tool in providing the bridge between respiratory therapist-driven protocols and closed-loop ventilation. It may provide respiratory therapists with the computer-driven, physiologically interactive equipment necessary to enhance weaning, thus enabling patients the opportunity to discontinue mechanical ventilation expeditiously.

This study found that the Automode algorithm did not increase measured WOB. The patient's WOB depends on pre-trigger and trigger factors such as patient effort to trigger and delay between trigger and response of the ventilator.[24] The ΔP, as an indication of the animal's effort to trigger, was greatest in the pre-paralysis period. The reason for this difference may be that the animals had not completely recovered from the paralytic agent when the ventilator again began to triggered by the animal. The animals were simply not able to exert as great a negative deflection as before being paralyzed. Having to pharmacologically paralyze the animals to induce apnea was not ideal, since this pharmacologic intervention would not normally be used clinically in this way. Clinically, patients would be on appropriate sedation, not paralytics, during the weaning phase, and any apnea episodes would depend on the disease process.

There was no significant difference in time from initiation of the breath to the maximum flow of each breath before or after the induced apnea. The lack of a disparity in time differences indicates that, although the animals were creating less negative pressure to obtain a breath post-paralysis, there was no increase in time necessary to reach maximum flow.

The amount of maximum flow decreased during the post-paralysis phase, and this difference was statistically significant for PC/PS and VC/VS. However, there was no difference in peak inspiratory flow among the modes. These decreases in flow may also be due to the paralytic agent. The reason that the maximum flow of PRVC/PS had less of a decrease than the other 2 modes studied is not clear, but may represent a type II error since the p value for PRVC/VS was trending toward statistical significance ($p = 0.173$).

The flow patterns acquired with the AcqKnowledge Biopac MP-100 information system did show differences before and after the support ventilation. Those differences may be explained by the residual effect of the neuromuscular blocking agent given to the animals to induce apnea and would not be a factor clinically.

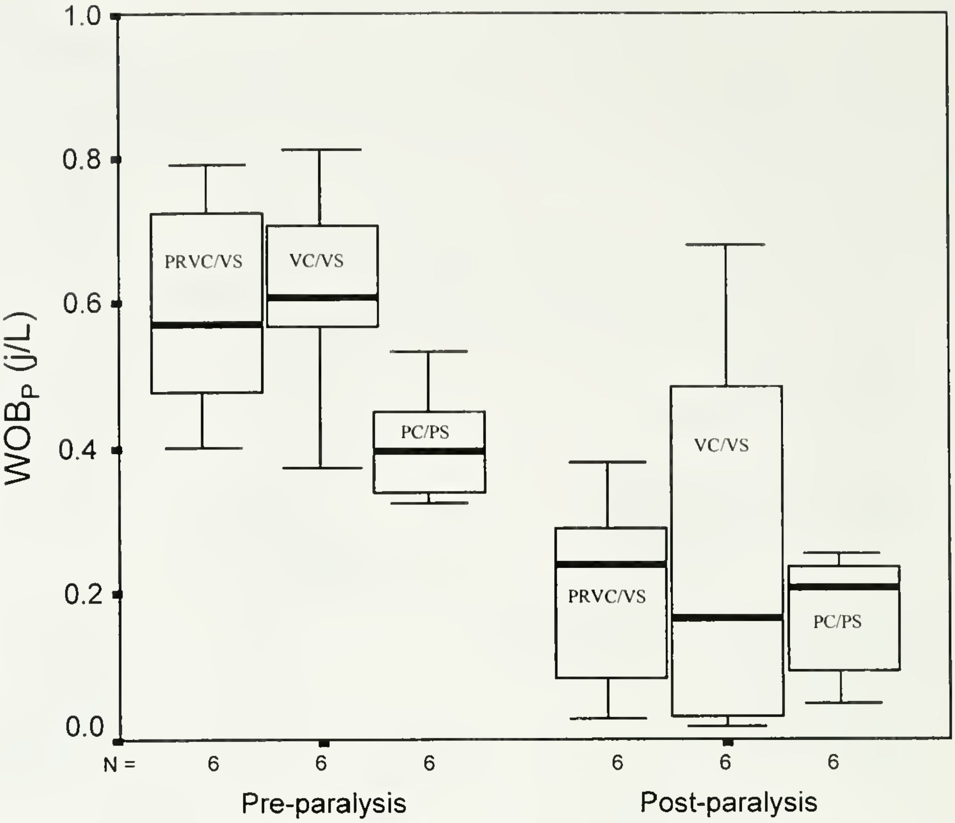

Fig. 5. Patient work of breathing (WOB$_P$), pre-paralysis and post-paralysis measurements for each mode. Each box plot shows the median, quartiles, and extreme values within a category. PRVC/VS = pressure-regulated volume control/volume support. PC/PS = pressure control/pressure support. VC/VS = volume control/volume support. p value < 0.05 for comparison of WOB$_P$ for PRVC/VS pre-paralysis and post-paralysis phase. p value < 0.05 for comparison of WOB$_P$ for VC/VS VS pre-paralysis and post-paralysis phase. p value < 0.05 for comparison of WOB$_P$ for PC/PS VS pre-paralysis and post-paralysis phase.

A limitation of this study is the necessity of paralytics to induce apnea. The use of this type of drug does not reflect the expected clinical pathway for a patient weaning from mechanical ventilation. But we felt it was the most reproducible method to allow us to induce apnea. The purpose of this study was to test the Automode algorithm and to determine whether it performed as advertised and to look at the impact on WOB when the switch to Automode occurred. Since WOB is most affected in the pre-trigger/trigger phase by changes in the degree of effort by the patient (most negative deflection of pressure measured at the airway) and the speed of response of the ventilator to the patient's needs, we focused our attention on those 2 factors. However, WOB and response time of the ventilator did not increase despite the use of a paralytic agent. Further, we measured $P_{0.1}$ and T_I/T_{TOT}. Respiratory drive ($P_{0.1}$) is a result of diaphragmatic contraction stimulated by neural drive. The clinical importance of this value, if elevated, represents an increase in work expenditure by the animal, or, if decreased, represents blunted respiratory drive. Blunted respiratory drive may be seen, for example, in our experiment with the use of neuromuscular blocking agent. Consequently, a low value for $P_{0.1}$ may indicate when respiratory drive is blunted, but $P_{0.1}$ is maintained up to 98% of somatic muscle paralysis.[25] In contrast, T_I/T_{TOT} is a measure of endurance and is defined as the ratio of the inspiratory time to the total time of the respiratory cycle. If respiratory muscles fatigue, more time is spent in inspiration, so T_I/T_{TOT} decreases. Theoretically, this may occur with the effects of neuromuscular blocking agents. However, our results did not show either value to reach a level of clinical importance after paralysis.

Another limitation to our study design may have been the dead space associated with the monitoring pneumotachographs and heat and moisture exchanger. The total dead space for our experimental setup was 22.14 mL (BiCore pneumotachograph 11 mL, Hans Rudolph pneumotachograph 8.74 mL, heat and moisture exchanger 2.4 mL). A potential limitation of our study design would be if dead space in our experimental setup caused increased arterial

Table 2. Mean Values from Measurements of Respiratory Variables

Measurement	Pre-Paralysis	Post-Paralysis	p Value
Pressure Regulated Volume Control/Volume Support (Ventilator Setting) (PRVC/VS)			
f (breaths/min)	22 ± 6	20 ± 2	0.463 (NS)
V_E (L/min)	2.25 ± 0.96	1.89 ± 0.50	0.345 (NS)
PIFR (L/min)	0.18 ± 0.02	0.20 ± 0.04	0.173 (NS)
PEFR (L/min)	0.13 ± 0.03	0.12 ± 0.01	0.463 (NS)
PIP (cm H_2O)	12.16 ± 2	13.24 ± 2	0.075 (NS)
WOB_V (j/L)	0.52 ± 0.20	0.87 ± 0.24	0.046
$P_{0.1}$ (cm H_2O)	3.75 ± 1.6	3.04 ± 1.6	0.345 (NS)
T_I/T_{TOT}	0.37 ± 0.8	0.75 ± 1.05	0.600 (NS)
Volume Control/Volume Support (Ventilator Setting) (VC/VS)			
f (breaths/min)	22 ± 5	19 ± 4	0.046
V_E (L/min)	2.26 ± 0.76	1.59 ± 0.32	0.028
PIFR (L/min)	0.20 ± 0.08	0.25 ± 0.11	0.600 (NS)
PEFR (L/min)	0.13 ± 0.03	0.12 ± 0.01	0.116 (NS)
PIP (cm H_2O)	12.19 ± 2	13.51 ± 3	0.116 (NS)
WOB_V (j/L)	0.50 ± 0.11	0.88 ± 0.27	0.028
$P_{0.1}$ (cm H_2O)	4.39 ± 1.4	2.54 ± 1.03	0.028
T_I/T_{TOT}	0.32 ± 0.52	0.33 ± 0.82	0.917 (NS)
Pressure Control/Pressure Support (Ventilator Setting) (PC/PS)			
f (breaths/min)	22 ± 6	18 ± 6	0.249 (NS)
V_E (L/min)	2.24 ± 0.79	1.59 ± 0.26	0.249 (NS)
PIFR (L/min)	0.19 ± 0.03	0.25 ± 0.17	0.753 (NS)
PEFR (L/min)	0.14 ± 0.02	0.12 ± 0.02	0.028
PIP (cm H_2O)	13.77 ± 2	14.10 ± 2	0.463 (NS)
WOB_V (j/L)	0.78 ± 0.07	0.95 ± 0.16	0.028
$P_{0.1}$ (cm H_2O)	3.38 ± 1.42	2.7 ± 1.1	0.173 (NS)
T_I/T_{TOT}	0.30 ± 0.96	0.31 ± 0.72	0.753 (NS)

Values are mean ± standard deviation.
NS = not significant
f = respiratory rate
V_E = minute ventilation
PIFR = peak inspiratory flow rate
PEFR = peak expiratory flow rate
PIP = peak inspiratory pressure
WOB_V = ventilator work of breathing
$P_{0.1}$ = respiratory drive
T_I/T_{TOT} = respiratory time fraction

carbon dioxide tension that increased respiratory drive. However, respiratory drive, as measured by $P_{0.1}$, was not clinically different before and after paralysis. Also, we have previously measured end-tidal carbon dioxide with the same equipment setup used during this experiment (eg, dead space), and found that end-tidal carbon dioxide was not elevated, and ranged between 38 and 45 mm Hg.

The SV300A is designed to meet the needs of neonatal, pediatric, and adult patients. Consequently, it provides distinctive flow ranges for each patient group. The apnea alarm time on the SV300A is predetermined by the patient range selector. For example, in the neonatal mode, the apnea alarm is 10 seconds, but in the pediatric range it is 15 seconds. In contrast, during Automode, if the patient cannot maintain spontaneous breathing, the ventilator shifts back to the control mode after 8 seconds in the pediatric range and 5 seconds in the neonatal range. A potential problem of Automode not reproduced in our study is the possible inability of the ventilator to match the patient's needs for flow with duration of the predefined time before switching back to the control mode. For example, the patient may need flow rates provided in the pediatric range but cycle time as defined in the neonatal range. Thus, there is a potential for hypercarbia. Offering the clinician the ability to match flow requirements and cycle time would enhance the ability to meet patient needs not already met by the SV300A. The addition of Automode may be an important contribution to the "weaning toolbox" already in place in intensive care units, but further clinical investigation is needed.

Conclusions

The initial information obtained during this experiment introduces other questions and concerns in the pediatric population, attesting to the need for this study to be done in the intensive care unit. Documentation with the AcqKnowledge Biopac MP-100 and BiCore systems pressure curves, flows patterns, and WOB for patients on Automode could be collected in the clinical setting.

The Automode algorithm performed as expected in this animal experiment and did not increase WOB. Our results indicate that patients might benefit from this new closed-loop ventilation technology.

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Call for Abstracts
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A Randomized, Controlled, Clinical Trial of a Chemically-Reactive Heated Humidifier

Shirley D Broach RRT and Charles G Durbin Jr MD FAARC

BACKGROUND: Inspired gases can be warmed and humidified in a variety of ways. The effect of a chemically-reactive heated heat and moisture exchanger/hygroscopic condenser humidifier (HME/HCH) on secretions, rate of core body warming, blood loss, and time to extubation was studied in hypothermic post-cardiac surgery patients. METHODS: Fifty patients with normal ventricular function, undergoing coronary bypass grafting, were randomized to receive either a conventional HME (Gibeck, Humid-Vent 1 [PN 11112], Hudson RCI, Temecula, California) or a chemically-heated HME (Thermax HCH Filter [PN 9302], Enternet Medical, Las Vegas, Nevada) following surgery or on arrival in the ICU. Effects on secretions, core temperature, postoperative bleeding, duration of intubation, and added resistance were measured. The Thermax weighs 67 g and adds 79 mL of dead space. The Humid-Vent 1 weighs 9.4 g and adds 10 mL of dead space. RESULTS: There was no significant difference between the 2 devices in time to extubation, blood loss, or quality or quantity of secretions. Use of the Thermax device, however, resulted in a more rapid rise in body temperature (0.299° C/h with the Thermax vs 0.073° C/h with the Humid-Vent 1, $p = 0.001$) and more added resistance (0.0672 cm $H_2O/L/s$ with the Thermax vs 0.0123 cm $H_2O/L/s$ with the Humid-Vent 1, $p = 0.00000172$). CONCLUSIONS: The Thermax chemically-heated HME results in more rapid warming of mildly hypothermic patients following cardiopulmonary bypass than does a conventional passive HME.

[Respir Care 2001;46(1):37–42] *Key words: hypothermia, humidification, active heat and moisture exchanger, HME, respiratory equipment, artificial airways, endotracheal tubes, cardiac surgery, intubation.*

Background

Breathing dry gases through an artificial airway results in heat and moisture loss from the lung as the inhaled gases are warmed and humidified to full saturation at body temperature by the time they reach the distal airways. Consequences of this process are increased energy expenditure, loss of body heat, drying of pulmonary secretions, inhibition of ciliary function, and systemic dehydration.[1] In extreme cases, patients develop thick pulmonary secretions that may lead to airway obstruction and infection. Proper conditioning of these inhaled gases should reduce patient morbidity.

Heated humidifiers (HH), heat and moisture exchangers (HMEs), and hygroscopic condenser humidifiers (HCHs) are commonly used methods for humidifying inspired gases. HHs provide warm, saturated gas at the artificial airway, but are bulky, require frequent caregiver attention to function properly, and may promote infection secondary to aspiration of water that rains out in the ventilator circuit. An HME/HCH is a simple passive device often used instead of an HH. When placed at the airway, it provides 60–80% of the necessary humidity by capturing some of the exhaled moisture and allowing it to be reused in subsequent breaths.[2,3] It may also function as a biological barrier by protecting the lower airway from external pathogens as well as containing the patient's respiratory flora and protecting the environment.[4,5]

HME/HCHs may be less costly to use than HH systems and are widely employed, often for longer than the manufacturers' recommendations.[6,7] However, an HME/HCH may increase dead space, work of breathing, and intrinsic positive end-expiratory pressure in spontaneously breath-

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Shirley Broach RRT presented a version of this paper at the 45th International Respiratory Congress, December 13–16, 1999, Las Vegas, Nevada.

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ing patients.[8] The efficacy of an HME/HCH appears reasonable in patients who do not have serious pulmonary disease or large amounts of thick secretions.[9,10]

Recognizing the limitations with conventional devices, several additional approaches to humidification have been developed. Combining a heated humidifier with a heated wire in the ventilator circuit (a heated wire circuit or HWC) reduces rainout and effectively maintains 100% relative humidity at the airway at a temperature approaching 34–35° C.[11] A serious complication from inadequate humidification is tracheal tube occlusion from inspissated secretions, which is less likely to occur with an HWC than with an HME/HCH.[12] High initial circuit cost and the need for continuous monitoring of these devices for efficacy are the downsides of the HWC. Another approach that has recently been suggested for improving airway gas humidification is to actively add heat to a passive HME/HCH device. Active heating of the exhaled and inhaled gases increases the efficiency of the HME/HCH technique to a point where it approaches the moisture delivered by an HWC. This is achieved with an electrical heating coil surrounding the HME/HCH, but this increases the cost, weight, and bulkiness, and may increase the likelihood of accidental extubation.

A novel way to actively heat and provide moisture to an HME/HCH takes advantage of the exothermic chemical reaction of converting expired carbon dioxide to calcium carbonate and water. The Thermax HCH combines chemically reactive Sodasorb and a conventional HME/HCH (Fig. 1 and Fig. 2). Exhaled carbon dioxide reacts with the Sodasorb to produce heat and moisture. Unlike a conventional, passive HME/HCH, inhaled moisture content and temperature are higher than exhaled moisture and temperature. This may result in added moisture not achievable with a passive HME/HCH. One possible benefit of this active HME/HCH device is in hypothermic patients, in whom warm, humidified inhaled gases can help raise reduced body temperature.

Hypothermic patients are at risk of medical complications, including coagulopathy, increased oxygen consumption, cardiac compromise, shivering, and discomfort. Following cardiac surgery employing hypothermia and cardiopulmonary bypass, patients are often returned to the intensive care unit (ICU) with low body temperature.[13] This may delay extubation, contribute to cardiac failure, and result in increased bleeding. In order to study the effectiveness of active HME/HCH therapy in preventing pulmonary complications and maintaining body temperature, we evaluated the effects of this novel HME/HCH on weaning, blood loss, secretion character, and body temperature rise, as well as calculating added respiratory resistance in moderately hypothermic patients following cardiac surgery. We used a conventional, passive HME as a control.

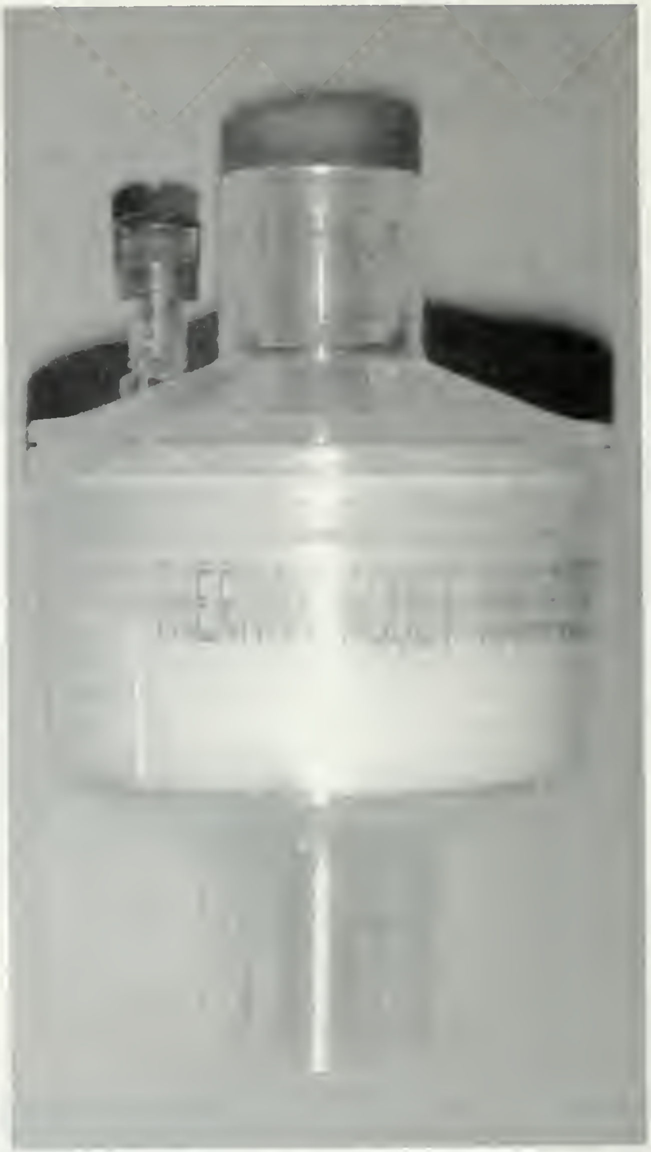

Fig. 1. The Thermax hygroscopic condenser humidifier.

Methods

The Human Investigation Committee of the University of Virginia allowed the study to proceed without written consent because the devices being evaluated are available for clinical use. We did, however, inform the patients and their caregivers of the purpose of the study and received verbal assent from the patients and their surgeons to participate. Fifty patients undergoing coronary artery bypass surgery and who had good preoperative ventricular function were enrolled. Patients were excluded if they had had previous open chest surgery, an ejection fraction less than 30%, underwent combined valve and coronary artery bypass grafting surgery, were under the age of 18, or expressed any reluctance to participate in research.

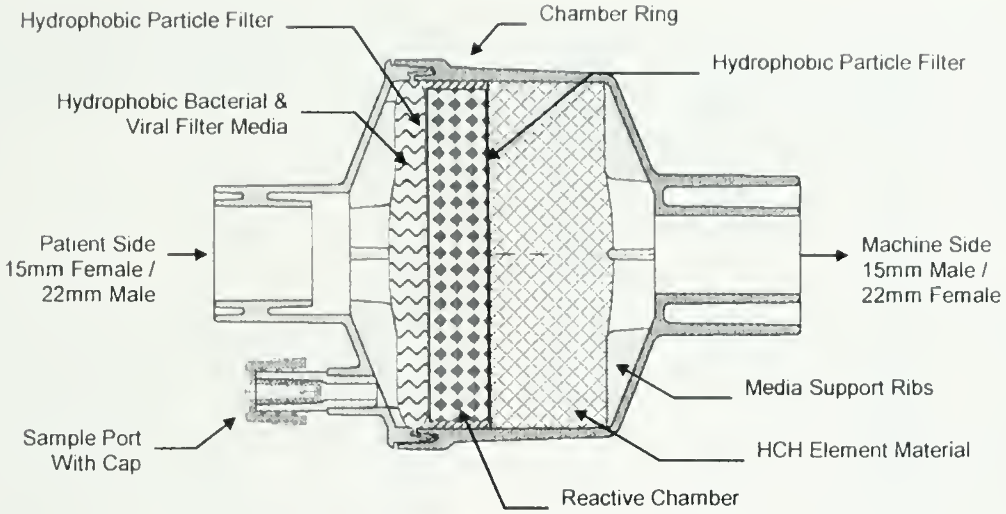
Hydrophobic Particle Filter
Chamber Ring
Hydrophobic Particle Filter
Hydrophobic Bacterial & Viral Filter Media
Patient Side 15mm Female / 22mm Male
Machine Side 15mm Male / 22mm Female
Media Support Ribs
Sample Port With Cap
HCH Element Material
Reactive Chamber

Fig. 2. Diagram of the internal components of the Thermax hygroscopic condenser humidifier.

Patients were randomly selected to receive either a Thermax HCH or a Gibeck Humid-Vent 1 HME at the completion of surgery or on arrival in the post-cardiac-surgery ICU. The anesthesiologist or the respiratory therapist caring for the patient selected an opaque, sealed envelope from a box initially containing 25 Gibeck and 25 Thermax labels inside to determine which device to use.

The following data were collected on each patient: time of ICU admission; admission core temperature (from the Swan-Ganz catheter); next recorded core temperature and time; time of extubation; duration of intubation; total chest tube drainage volume; secretion amount (none, modest, moderate, large) and quality (thin, thick, crusting); number of devices used per patient; peak and plateau airway pressure; and peak inspiratory flow with and without the test device in the circuit at the time of extubation. Calculated variables were: duration of intubation, rate of core temperature rise (degrees per hour), and airway resistance imposed by the HME/HCH. The latter was calculated by taking the difference in the following equation with and without the HME/HCH, under constant flow, volume ventilation:

$$(\text{peak pressure} - \text{plateau pressure})/\text{peak flow}$$

Continuous variables were tested for significance using 2-tailed *t* tests; discrete variables were compared using chi-square analysis. Statistical significance was set at $p < 0.05$.

Results

Only 46 of the 50 studied patients (22 with the Thermax HCH and 24 with the Gibeck HME) had all required data available for analysis. The following groups were used in the subsequent analysis: Group T (the 22 patients treated with the Thermax HCH) and Group G (the 24 patients treated with the Gibeck HME). Table 1 summarizes the data. There was a slight (nonsignificant) difference in initial temperature between the 2 groups on arrival in the ICU (values are mean ± SD): Group T averaged 36.0 ± 0.68° C and Group G averaged 36.3 ± 0.66° C (p = 0.134).

There was no difference in average amount of chest tube drainage (429 ± 347 mL in Group T vs 382 ± 275 mL in Group G, p = 0.608), time to extubation (10.11 ± 5.45 h in Group T vs 8.52 ± 3.41 h in Group G, p = 0.237), or quality or quantity of secretions.

No HME/HCH in either group became clogged or needed to be changed for any reason. There were no inadvertent extubations.

The rate of rise of core temperature was significantly greater in Group T (0.299° C/h) than in Group G (0.073° C/h) (p = 0.0027). There was more added resistance from the HME/HCH in Group T (0.0672 ± 0.036 cm H_2O/L/s) than in Group G (0.0123 ± 0.029 cm H_2O/L/s) (p = 0.00000172).

Though the average time between arrival in the ICU and the next recorded core temperature was similar between the two groups (2.2 ± 1.29 h in Group G vs 2.27 ± 1.15 h in Group T, p = 0.824) the range was from 30 minutes to almost 6 hours. In order to eliminate the possibility that several patients with long time intervals between temperature measurements influenced the results, patients who had their second temperature recorded more than 2 hours following their arrival in the ICU were removed from the analysis. The rate of temperature rise was 0.37° C/h in Group T and 0.06° C/h in Group G, which remained sig-

Table 1 Patient Data

Patient Number	Group	Initial Temperature (° C)	Next Temperature (° C)	Time to Next Temperature (h)	Rate of Temperature Rise (° C/h)	Extubation Temperature (° C)	Time to Extubation (h)	Chest Tube Drainage (mL)
1	G	36.9	37.8	3.8	0.24	37.8	4.5	148
2	G	34.9	35.4	1.8	0.29	36.6	6.9	370
3	G	36.9	37.4	1.3	0.38	37.1	13.6	280
4	G	36.6	37.2	4.3	0.14	37.2	6.6	368
5	G	37.6	37.5	1.0	−0.10	37.8	19.8	1075
6	G	36.5	36.6	1.4	0.07	37	7.3	220
7	G	36.6	36.4	1.8	−0.11	37.2	5.0	196
8	G	36.4	36.4	0.2	0.00	37	10.8	380
9	G	36.7	37.1	3.0	0.13	37.4	7.0	265
10	G	36.4	36.3	2.6	−0.04	37.3	13.3	440
11	G	35.8	36.1	2.1	0.14	36.7	10.5	545
12	G	36.3	36	2.5	−0.12	36.9	7.0	270
13	G	36.7	36.5	0.7	−0.30	36.8	8.0	300
14	G	36.7	36.7	1.2	0.00	37.4	5.9	45
15	G	35.3	35.3	1.5	0.00	36.7	9.7	665
16	G	35.8	36	1.3	0.15	36.8	7.3	275
17	G	36	36	1.6	0.00	37.3	6.0	170
18	G	36.8	37.8	5.8	0.17	37.7	6.3	261
19	G	36.6	36.7	1.8	0.06	37	7.5	340
20	G	36.4	36.5	2.3	0.044	37.4	6.3	270
21	G	36.1	36.6	1.8	0.27	36.6	9.0	650
22	G	34.9	35	1.7	0.06	36.7	7.5	192
23	G	35.3	36.2	3.0	0.30	37.1	11.8	1200
24	G	36.6	36.5	4.3	−0.02	36.4	7.3	250
Average ± SD		36.28 ± 0.66	36.5 ± 0.73	2.19 ± 1.29	0.073 ± 0.157	37.08 ± 0.39	8.52 ± 3.40	382 ± 275
25	T	34	35	1.3	0.80	37.5	6.9	320
26	T	36.3	36.6	2.0	0.15	37.1	5.0	725
27	T	36	37.1	3.8	0.29	37.6	22.0	1835
28	T	36	37	1.8	0.55	36.8	18.9	320
29	T	36.4	36.5	2.3	0.04	36.7	9.3	210
30	T	36.6	36.5	0.9	−0.11	37	7.7	440
31	T	35.8	37	1.3	0.90	37.1	7.5	136
32	T	36.1	36.5	2.2	0.18	36	7.5	470
33	T	35.9	36.3	2.1	0.19	37	13.5	350
34	T	36	37.2	1.9	0.63	37.4	6.8	425
35	T	36.8	37	5.3	0.04	37.5	19.9	570
36	T	36.2	36.7	1.4	0.35	37.2	7.1	336
37	T	36.1	37.1	2.3	0.44	37.1	5.3	225
38	T	35.9	36	0.5	0.20	36.8	7.3	369
39	T	36	37	2.0	0.50	36.7	21.0	360
40	T	34.5	35.1	1.1	0.55	37.5	9.6	345
41	T	35.7	35.4	3.2	−0.09	35.4	3.2	345
42	T	37.1	37.1	1.8	0.00	37.2	6.8	133
43	T	35.9	36.2	2.0	0.15	37.4	8.0	250
44	T	36	37	3.7	0.27	37.3	9.2	202
45	T	35.6	36.8	3.8	0.32	36.8	8.2	574
46	T	36.7	37.5	3.5	0.23	37.5	11.8	514
Average ± SD		35.98 ± 0.66	36.57 ± 0.68	2.27 ± 1.15	0.299 ± 0.271	37.03 ± 0.52	10.11 ± 5.45	430 ± 347

nificantly different in this subgroup comparison ($p = 0.0023$).

To minimize the effect of a high initial temperature (which could result in a reduced rate of rise in temperature), patients with initial temperatures greater than 36° C were removed. In the remaining 20 patients, the rate of core temperature rise was 0.40° C/h in Group T and 0.13° C/h in Group G, which remained significantly different ($p = 0.0273$).

Discussion

Heated humidifiers are more effective than passive HME/HCHs at delivering heat and moisture to patients with artificial airways.[14] The added heat they provide is sometimes used to promote rewarming of hypothermic patients.[15,16] While passive HME/HCHs are used to decrease core temperature loss during anesthesia, actual heat gain from an HME/HCH is not expected. We were surprised that this simple, chemically-heated HME/HCH was actually able to more rapidly increase body temperature in mildly hypothermic patients following cardiac surgery. This may be of substantial value to hypothermic patients following cardiac surgery. However, we were unable to demonstrate that this more rapid warming resulted in any clinically relevant improvement in measured outcomes related to extubation or bleeding, as a measure of coagulation abnormality. This is probably because there are more important variables influencing these outcomes.

In regard to timing of extubation, level of consciousness or time of day exert more influence on the decision to extubate than does restoration of core body temperature. It is possible that these patients benefited in other ways not measured. It is known that spontaneous warming from hypothermia may result in increased oxygen consumption, shivering, and cardiac ischemia. We did not record shivering or examine the cardiograms for ischemia. Hypothermic patients are actively warmed in the ICU following cardiac surgery. By protocol, all patients with core temperatures of ≤ 36.5° C are treated with heating lamps (two 400 Watt heat lamps are placed at a distance of 100 cm) but no other heating methods. When core temperature exceeds 36.5° C, the lights are removed. The room temperature remains at 25–26° C and fluids are not warmed. This protocol was applied identically to both groups.

We noted a 5-fold increase in airway resistance imposed by the Thermax device, compared to the HME manufactured by Gibeck. The manufacturer reports resistance as less than 2.5 cm H_2O drop at 60 L flow across the device. While the difference in resistance between the 2 devices is statistically significant, the actual resistance is not clinically important, as it is 10 to 20 times less than the resistance of breathing through an endotracheal tube or the normal upper airway.[17]

The internal dead space added by the Thermax device is reported by the manufacturer to be 79 mL, which is much larger than that reported for the comparison HME from Gibeck—only 10 mL. This would be a major problem for pediatric patients.

The weight of the Thermax HCH is also substantially greater (67 g) than the Gibeck HME (9.4 g). This may increase the risk of extubation, but we observed no unplanned extubations in our trial. The Thermax device we tested is only recommended for use in adult patients, but according to the manufacturer a smaller, pediatric device is planned.

Our study did not answer several important clinical and economic questions. Clinical uncertainties still to be answered include the effectiveness of this device in humidifying inspired gas and how well it works after an extended period of time. According to manufacturer-generated data, the device produces an adequate amount of warmth and moisture during short-term use. The maximum temperate output is reported to be 38.5 C, below the threshold for pulmonary thermal damage.[18] The manufacturer recommends that the device be replaced every 24 hours, which is true for all passive HMEs as well. With current trends to extend the use of all equipment, the Thermax HCH humidification effectiveness must be evaluated at 24 hours and beyond.

The device contains particle, bacterial, and viral filters and should provide adequate infectious disease protection to the patient and caregivers.

Economic issues include direct cost comparisons. The retail list price of the Thermax HCH is $290.00/case of 50, whereas the Gibeck Humid-Vent 1 is $141.60/case of 50. However, these price comparisons are not realistic, as the distributor prices are considerably lower and end users rarely pay full price. In addition, a realistic cost analysis must estimate the frequency of change and the potential or actual savings in ICU time, treatments, or avoidance of complications.

If considering using the tested device, another subject for consideration is the large size of the device itself and the substantial dead space added. Patients may need to have minute ventilation increased to compensate for the increased dead space.[19]

Finally, we did not observe any effect on secretion quality or quantity, probably because of the "healthiness" of this test population. The effectiveness of the device in providing airway humidity is the proposed advantage of the device, not its effect on body temperature. According to tests performed by the manufacturer, it provides up to 47.25 mg H_2O/L output, compared to around 34 mg H_2O/L from a conventional device or even an HH. An important benefit may be seen in patients more prone to thick secretions than was our test population, or if the device is used for a longer time. More clinical studies, in patients who produce more secretions, are needed to define the role of this device in airway care.

Conclusions

The Thermax chemically-heated HME results in more rapid warming of mildly hypothermic patients following cardiopulmonary bypass than does a conventional passive HME.

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Nebulization of a Suspension of Budesonide and a Solution of Terbutaline into a Neonatal Ventilator Circuit

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METHODS: The amount of nebulized budesonide and terbutaline delivered through an endotracheal tube (ETT) was measured in vitro using a test lung and filters in a neonatal ventilator circuit. Budesonide suspension (1 mg) was used in a concentration of 0.5 mg/mL and terbutaline solution (5 mg) in a concentration of 2.5 mg/mL. RESULTS: The median amount of terbutaline deposited on the inspiratory filters was significantly higher than that of budesonide: 0.4% vs 0.3% of the nominal doses with the nebulizer connected 8 cm upstream of the ETT and nebulization performed in a constant output mode (setup A), and 2.8% vs 1.0% with the nebulizer connected directly to the ETT and nebulization performed in a breath-synchronized mode (setup B) ($p < 0.05$ for both). The corresponding amounts of drug deposited on the waste filters with setup A were 19.2% for terbutaline and 12.6% for budesonide, and with setup B 16.2% for terbutaline and 6.2% for budesonide ($p < 0.05$ for both). CONCLUSIONS: The ratio between drug delivery to the inspiratory and waste filters, describing the relationship between lung deposition and wastage of drug to the ventilator circuit, was setup-dependent but not drug-dependent. The ratio with setup A was 0.02 for both budesonide and terbutaline. The respective ratios were significantly ($p < 0.05$) higher for budesonide (0.16) and for terbutaline (0.17) with setup B. The differences in the delivered doses of the two drugs through the ETT seems to be a function of both the drug formulation and the nebulizer-ETT setup. With the nebulizer connected directly to the ETT and nebulization in breath-synchronized mode, the differences between the two drugs were enhanced, compared with the nebulizer connected upstream of the ETT and nebulization in constant output mode. The results indicate that a solution is superior to a suspension in terms of drug delivery through an ETT.

[Respir Care 2001;46(1):43–48] *Key words: Budesonide suspension, terbutaline solution, endotracheal tube, in vitro, neonates, nebulization, inhalation therapy.*

Background

The delivery of aerosolized drugs offers several advantages for the treatment of infants with ventilator-dependent lung disease. Compared to systemic treatment, better targeting of the aerosolized drug affords rapid onset of the pharmacologic effect through high topical drug concentration, with fewer systemic effects. However, a number of factors may affect the dose of the drug deposited in the lungs, including ventilatory variables, size of the endotracheal tube (ETT), position of the nebulizer in the ventilator circuit, and mode of nebulization (ie, constant output or breath-synchronized).[1,2]

The delivered dose of budesonide suspension through the ETT has been shown to vary depending on both the position of the jet nebulizer in the ventilator circuit and the mode of nebulization.[2] During nebulization in constant output mode, the amount of budesonide delivered through the ETT increased from a median of 0.3% to 0.7% of the nominal dose, depending on whether the nebulizer was connected 8 cm upstream from the ETT connector (0.3%) or connected directly to the ETT (0.7%). With the nebulizer connected directly to the ETT, the amount of budesonide delivered through the ETT increased from a median of 0.7% to 1.1%, depending on whether nebulization was constant (0.7%) or synchronized to the inspiratory phase (1.1%).

Recent data indicate that the formulation of a nebulized drug (ie, suspension or solution) influences the drug output

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from a nebulizer.[3] The total outputs of nebulized budesonide and terbutaline were 42.8% and 58.8%, respectively, of the nominal doses following breath-synchronized jet nebulization in healthy adult subjects.[3] The difference was probably a consequence of the fact that all aerosol droplets leaving the nebulizer might contain terbutaline, whereas the micronized budesonide, with a mean primary particle size of about 2.4 μm, would fit only into droplets larger than the budesonide particles.[4] Thus the amount of nebulized drug delivered through the ETT would most likely also be formulation-dependent. To address this issue we designed an in vitro study to compare the amounts of budesonide (suspension) and terbutaline (solution) delivered through an ETT using 2 in vitro setups. The 2 setups would be identical to the ones producing delivered doses of 0.3% and 1.1% of budesonide suspension in our previous study.[2] We hypothesized, based on previous data,[3] that the in vitro delivery of a solution of terbutaline through an ETT would be about 50% higher than the delivery of a suspension of budesonide, irrespective of the in vitro test setups.

Methods

Equipment

The treatment situation of a ventilated premature neonate was mimicked with a rubber silicone test lung (Dräger Medizintechnik GmbH, Lübeck, Germany) with a compliance of approximately 0.94 mL/cm H_2O, and a time-cycled, pressure-limited Baby Bird ventilator (Bird Corporation, Palm Springs, California) with a continuous gas flow of 12 L/min. The inspiratory pressure was set to 18 cm H_2O, with a positive end-expiratory pressure of 2 cm H_2O. The ventilation frequency was set to 40 breaths/min, giving a tidal volume of 15 mL and a minute volume of 0.6 L. The duration of inspiration was 0.4 seconds and the total respiratory cycle was 1.5 seconds, giving an inspiratory-to-expiratory time ratio of 0.27. An ETT (Portex, Hythe, United Kingdom) 11 cm in length and with an outer diameter of 3.0 mm was connected to the circuit. No humidifier was used. A Bird jet nebulizer was run with a compressed gas flow of 4.5 L/min through the nebulizer. Aerosolized drug was collected on 2 filters (Marquest MQ-303 viral filter, Marquest Medical Products, Englewood, Colorado), one positioned between the tip of the ETT (inspiratory filter) and test lung and the other in the expiratory line of the ventilator circuit at a distance of 8 cm from the ETT (waste filter). The ventilator settings and choice of compressed gas flow, but not the jet nebulizer, were identical to the ones in our previous in vitro study of nebulized budesonide suspension.[2]

Test Setups

The delivery of budesonide and terbutaline was investigated using 2 different test setups, shown schematically in Figures 1A and 1B. In both setups the nebulizer was connected to the circuit by a T-piece connector with a dead space volume of 5 mL. In setup A (see Fig. 1A) the nebulizer was inserted into the inspiratory line of the ventilator circuit at a distance of 8 cm upstream from the ETT connector, and the nebulizer was run in a constant output mode. In setup B (see Fig. 1B) the nebulizer was connected directly to the ETT and run in a breath-synchronized mode with the nebulizer triggered at the beginning of each inspiration to produce aerosol during 0.3 second of the inspiration. Breath-synchronization was achieved with a modified Spira Elektro 4 synchronizer (Respiratory Care Center, Hämeenlinna, Finland).

Six experiments were performed with each setup and drug, for a total of 24 experiments. The same nebulizer was used in all tests. The nebulizer was charged with 1.0 mg of budesonide suspension (0.5 mg/mL, 2 mL suspension) or with 5 mg of terbutaline solution (2.5 mg/mL, 2 mL solution). Both drugs were nebulized to dryness, which corresponded to a gravimetric output of 1.5 g (ie, to 75% of the weight of the 2 mL volume). The gravimetric output was kept constant at 1.5 g in all the tests. The duration of nebulization was recorded. Between the tests the nebulizer cup was washed with ethanol and dried.

Budesonide was eluted from the filters with a water ethanol solution, and terbutaline was eluted with a sulphuric acid solution. The concentration and mass of budesonide and terbutaline were determined by reversed-phase high-performance liquid chromatography at the analytical chemistry department, AstraZeneca, Lund, Sweden.

Statistical Analyses

Differences between the delivery of budesonide and terbutaline were analyzed with the nonparametric Mann-Whitney test. The same test was used to compare the effect of the different setups on the delivery of the drugs. Differences were considered significant if p was < 0.05.

Results

Inspiratory Filters

With test setup A the median amount of budesonide deposited on the inspiratory filters was 3 μg (range 2–3 μg). This corresponded to 0.3% (range 0.2–0.3%) of the nominal dose of 1.0 mg of budesonide suspension. The median amount of terbutaline deposited on the inspiratory filters in setup A was 20 μg (range 20–30 μg), corre-

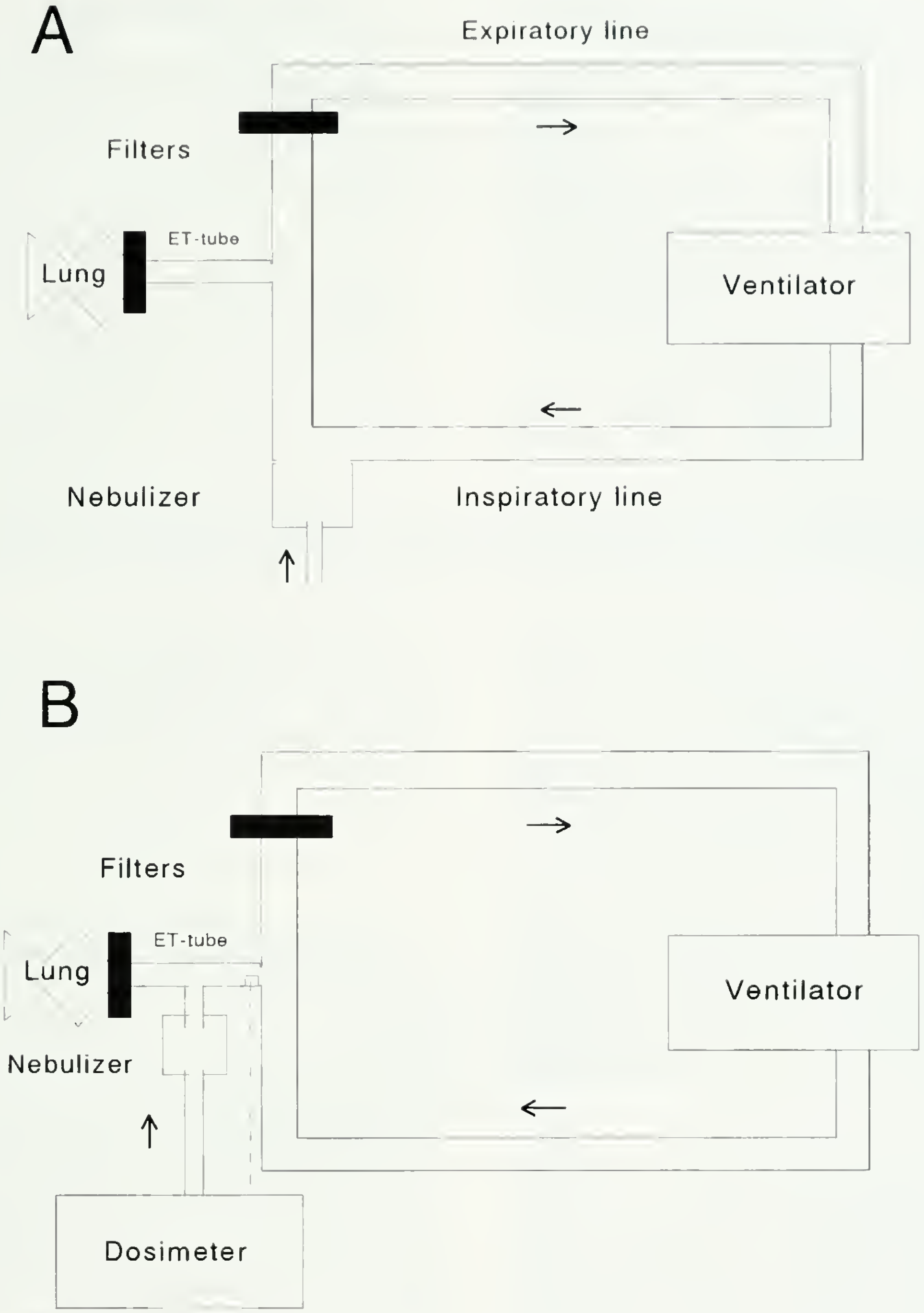

Fig. 1. The experimental setups. The nebulizer connected into the inspiratory line in setup A (constant flow) and to the endotracheal tube (ET tube) in setup B (breath-synchronized flow). Arrows indicate the direction of gas flow. Black bars indicate the positions of the filters.

sponding to 0.4% (range 0.4–0.6%) of the nominal dose of 5.0 mg terbutaline solution.

With test setup B, the median amount of budesonide deposited on the inspiratory filters was 10 μg (range 9–13 μg), corresponding to 1.0% (range 0.9–1.3%). The median amount of terbutaline delivered to the inspiratory filters was 140 μg (range 110–160 μg), corresponding to 2.8% (range 2.2–3.2%).

Calculated as a percent of the nominal doses, the deposition of terbutaline on the inspiratory filters was significantly higher than the deposition of budesonide, for both setups (Fig. 2A, $p < 0.05$ for both setups). The combina-

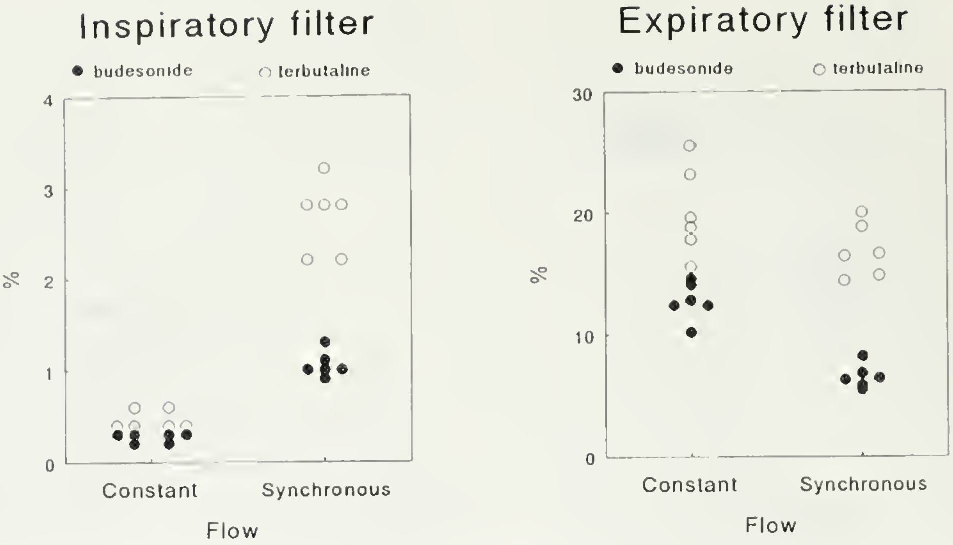

Fig. 2. Terbutaline and budesonide mass as a percent of the nominal dose. The delivery of terbutaline to the inspiratory and waste filters was significantly higher than the delivery of budesonide, both with constant and breath-synchronized flow ($p < 0.05$ for all).

tion of breath-synchronized nebulization and the nebulizer connected directly to the ETT (setup B) resulted in a significantly higher inspiratory filter deposition of both budesonide and terbutaline than with the combination of constant output nebulization and the nebulizer connected upstream from the ETT (setup A) ($p < 0.05$ for both drugs).

Waste Filters

With test setup A the median amount of budesonide deposited on the waste filters was 124 μg (range 102–146 μg), corresponding to 12.0% (range 10.0–15.0%). The median dose of terbutaline deposited on the waste filters was 960 μg (range 780–1,280 μg), corresponding to 19.2% (15.6–25.6%).

With test setup B the median amount of budesonide deposited on the waste filters was 64 μg (6.0%), range 55–82 μg (6.0–8.0%). The median dose of terbutaline deposited on the waste filters was 825 μg (16.5%), range 720–1,000 μg (14.4–20.0%).

Calculated as a percent of the nominal doses, the deposition of terbutaline on the waste filters was significantly higher than the deposition of budesonide, for both setups (Fig. 2B, $p < 0.05$ for both setups). With test setup A, the ratio between drug deposited on the inspiratory and waste filters, describing the relationship between the deposition in the lung and the wastage of the drug to the ventilator circuit, was 0.02 for both budesonide (3 μg:124 μg) and terbutaline (20 μg:960 μg). With test setup B the respective ratios were significantly ($p < 0.05$) higher for both budesonide (10 μg:64 μg, ratio 0.16) and terbutaline (140 μg:825 μg, ratio 0.17).

The median duration of the constant output nebulization was 3.9 minutes for budesonide and 3.6 minutes for terbutaline (not significant). The respective durations of the breath-synchronized nebulization were 36.9 minutes and 35.0 minutes (not significant).

Discussion

Our hypothesis was that the in vitro delivery of a solution of terbutaline through an ETT would be about 50% higher than the delivery of a suspension of budesonide, irrespective of test setup. We based this hypothesis on the results from an in vivo study with the same drugs but with a different jet nebulizer and no ETT.[2] The results of the present study showed that the delivery of terbutaline through an ETT was superior to the delivery of budesonide. The difference in drug delivery with test setup A was smaller than hypothesized (0.4% vs 0.3%), whereas the difference with test setup B was several times larger than hypothesized (2.8% vs 1.0%), both results indicating that the drug delivery through the ETT was a function of both the drug formulation and the nebulizer-ETT setup.

In vitro drug delivery through the ETT has been documented using various nebulizers and test setups and ranged from 0.02% to 2.7% of the nominal dose of drug.[2,5–10] Because of differences in test setups, all the results cannot be directly compared with our results. There is, however, previous evidence supporting our findings that in vitro drug delivery to the ETT decreases with increasing length of tubing between nebulizer and ETT[11,12] and that connecting the nebulizer directly to the ETT increases drug delivery through the ETT.[2,11,13] Drug delivery through the

ETT has also been shown to be dependent on the diameter of the ETT.[14]

A humidifier was not used in our study, because it could have decreased drug delivery through the ETT by increasing the size of the droplets. The connection of the nebulizer directly to the ETT added a dead space of 5 mL in our in vitro test setups. The increased dead space might, however, be functionally compensated for by the flow of fresh gas to the connector.[2]

With setup A the difference in drug delivery through the ETT was minimal between budesonide and terbutaline (0.3% and 0.4%, respectively), indicating that the length of the tubing between the nebulizer and the ETT was more important than drug formulation issues. When the length of tubing was eliminated as a confounding factor in setup B, the difference in drug delivery between budesonide and terbutaline increased (1.0% and 2.8%, respectively). The increase in drug delivery between the setups was about 3-fold for budesonide, but 7-fold for terbutaline. The large difference in drug delivery through the ETT with setup B was probably a result of both differences in total nebulizer drug output and the droplet cut-off properties of the ETT. In our previous study of nebulized budesonide delivery through the ETT, the droplet mass median diameter of 3.4 μm measured at the nebulizer mouthpiece decreased to 2.1 μm when measured at the end of the ETT.[2] Because micronized budesonide has a primary particle size of about 2.4 μm,[4] the 3 mm diameter ETT would decrease the amount of budesonide passing through the tube more profoundly than the amount of terbutaline.

Interestingly, the ratio between drug delivery to the inspiratory and waste filters, describing the relationship between lung deposition and wastage of drug to the ventilator circuit, was setup-dependent, not drug-dependent. The efficacy ratio was 0.02 for both budesonide and terbutaline for setup A. The respective ratios were significantly higher but similar for both budesonide (0.16) and terbutaline (0.17) for setup B. Our findings of the differences in the efficacy/wastage ratio between the comparable setups are also in agreement with previously published results.[2]

Is a lung deposition of 0.3–2.8% then clinically relevant? Recent data from a large clinical study in young asthmatic children showed good effect versus placebo but no dose-response for nebulized budesonide in nominal doses of 250 μg bid, 500 μg bid, and 1,000 μg bid.[15] In 3–6-year-old children these nominal doses of nebulized budesonide would correspond to mean lung depositions[16] of about 10 μg, 20 μg, and 40 μg, respectively. Assuming a mean skin surface area of 0.8 m^2 in these children, the lung deposition would correspond to 12.5 $\mu g/m^2$, 25 $\mu g/m^2$, and 50 $\mu g/m^2$ skin surface area. The skin surface area in pre-term infants of 1 kg weight is about 0.12 m^2, and, using the lowest clinically relevant nominal dose of 250 μg of budesonide, the lung-deposited dose would be about 1.5 μg (12.5 $\mu g/m^2$). With setup A this could be achieved by a nominal dose of 500 μg budesonide, whereas with setup B a nominal dose of 125 μg budesonide would be sufficient. The same kind of reasoning can be applied to terbutaline.

Comparisons between in vivo and in vitro test setups have shown that in vitro setups similar to the setups used in our in vitro study tend to overestimate the drug delivery.[13] This is mainly because of the function of the inspiratory filter in the in vitro setup, in which the inspiratory filter captures the total amount of aerosolized drug during inspiration, including the part of the aerosol that would be exhaled during expiration. This has been observed in various setups, including antimicrobial agents and glucocorticoids in ventilated and nonventilated subjects.[17–21] However, aerosol deposition on inspiratory filters in an in vitro bench model has been found to be proportional to the deposition detected in an animal lung.[13] Thus, allowing for a slight setup-dependent overestimation of the drug delivery, the neonatal in vitro test setup can be used for the estimation of drug delivery through the ETT in real treatment situations.

Conclusions

The present results suggest that the distribution of nebulized terbutaline and budesonide in the ventilator tubing (ie, waste filter) and through the ETT (ie, inspiratory filter) depends on the efficacy ratio of the nebulizer system in the neonatal ventilator circuit. A marked increase in this ratio may be achieved by using breath-synchronized nebulization and by placing the nebulizer directly at the ETT. The results indicate that a solution of terbutaline is superior to a suspension of budesonide in terms of drug delivery through an ETT.

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Lung Collapse during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

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BACKGROUND: Current ventilator management for acute respiratory distress syndrome (ARDS) incorporates low tidal volume (V_T) ventilation in order to limit ventilator-induced lung injury. Low V_T ventilation in supine patients, without the use of intermittent hyperinflations, may cause small airway closure, progressive atelectasis, and secretion retention. Use of high positive end-expiratory pressure (PEEP) levels with low V_T ventilation may not counter this effect, because regional differences in intra-abdominal hydrostatic pressure may diminish the volume-stabilizing effects of PEEP. CASE SUMMARY: A 35-year-old man with abdominal compartment syndrome (intra-abdominal pressure > 48 cm H_2O) developed ARDS and was treated with V_T of 4.5 mL/kg and PEEP of 20 cm H_2O. Despite aggressive fluid therapy, appropriate airway humidification and tracheal suctioning, the patient developed complete bronchial obstruction, involving the entire right lung and left upper lobe. After bronchoscopy the patient was placed on a higher V_T (7.0 mL/kg). Intermittent PEEP was instituted at 30 cm H_2O for 2 breaths every 3 minutes. This intermittently raised the end-inspiratory plateau pressure from 38 cm H_2O to 50 cm H_2O. With the same airway humidity and tracheal suctioning practices bronchial obstruction did not reoccur. CONCLUSION: Low V_T ventilation in ARDS may increase the risk of small airway closure and retained secretions. This adverse effect highlights the importance of pulmonary hygiene measures in ARDS during lung-protective ventilation. [Respir Care 2001;46(1):49–52] *Key words: lung collapse, acute respiratory distress syndrome, low tidal volume ventilation, positive end-expiratory pressure, ARDS, PEEP, atelectasis, secretion retention.*

Introduction

Acute respiratory distress syndrome (ARDS) manifests as a diffuse, unevenly-distributed injury in which substantial portions of the lung are normal.[1] As a result, mechanical ventilation with high tidal volume (V_T) may cause repeated regional over-distention, inducing lung injury in previously normal tissue.[2] Therefore, current ventilator management for ARDS combines low V_T ventilation with permissive hypercapnia.[3] In supine subjects, low V_T ventilation is associated with progressive atelectasis and decreased respiratory system compliance (C_{RS}),[4,5] primarily because of small airways closure due to regional differences in transmitted intra-abdominal hydrostatic pressure.[6] As a result, a small V_T delivered with controlled mechanical ventilation is preferentially distributed to the ventral portions of the lung, where intra-abdominal pressure is least.[6] Moreover, high levels of positive end-expiratory pressure (PEEP) may not stabilize lung volume in dorsal regions, where transmitted intra-abdominal pressure is higher.[7] Decreased C_{RS} during low V_T ventilation appears to be more pronounced during eucapnia and hypercapnia.[5]

In addition, increased lung volume is considered crucial to pulmonary hygiene.[8] Transient hyperinflation is generally recommended[8,9] as an adjunct to suctioning because it is thought to promote secretion clearance by increasing the

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expiratory flow from a higher end-inspiratory volume.[9] Therefore, using low V_T ventilation in ARDS without providing for transient pulmonary hyperinflation may result in persistent atelectasis and the risk of retained secretions. We report a case of complete lung collapse during low V_T ventilation in a complicated case of ARDS.

Case Summary

The patient was a 35-year-old male with severe hemorrhagic pancreatitis and abdominal compartment syndrome.[10] He developed ARDS 5 days following emergency surgery to relieve intra-abdominal hypertension (intra-abdominal pressure > 48 cm H_2O) resulting in cardiovascular collapse. Lung-protective ventilation was initiated at a V_T of 6 mL/kg of predicted body weight, using a Dräger E-2 Dura ventilator (Dräger, Telford, Pennsylvania). A continuous low flow (3 L/min) pressure-volume curve was constructed to identify the critical alveolar opening pressure by determining the lower inflection point (LIP).[11] LIP was identified at 22 cm H_2O using the method described by Lu et al.[12] However, the applied PEEP was limited to 20 cm H_2O because of hemodynamic instability. Intrinsic PEEP was 2–5 cm H_2O above the applied PEEP. Ascitic fluid continuously leaked through the patient's open abdominal wall, requiring frequent dressing changes that resulted in prolonged decreases in S_{pO_2} (oxygen saturation measured via pulse oximetry). Between ARDS days 1 and 5, the delivered V_T was decreased to 4.5 mL/kg to limit end-inspiratory plateau pressure (P_{plat}) to 40 cm H_2O. LIP remained at 22 cm H_2O on ARDS day 5.

Between ARDS days 3 and 7, clinicians intermittently documented aspiration of scant to small amounts of either yellow or green sputum that ranged from slightly-thick to thick. Microbiological exam of tracheal aspirates revealed rare *Streptococcus pneumoniae* and *Klebsiella pneumoniae* that were not associated with either fever or a new pulmonary infiltrate. The patient was receiving imipenem and no adjustment was made to his antibiotic therapy. By ARDS day 8, the ratio of arterial oxygen tension-to-fractional concentration of inspired oxygen (P_{aO_2}/F_{IO_2}) had risen to 198 mm Hg on F_{IO_2} 0.50 and PEEP of 20 cm H_2O. Ventilation was maintained at 4.5 mL/kg, with a P_{plat} of 35 cm H_2O.

However, during routine care on ARDS day 8, the patient was turned and his S_{pO_2} abruptly fell to 65%. On an F_{IO_2} of 1.0 and PEEP of 20 cm H_2O, P_{aO_2} was 45 mm Hg. The peak airway pressure rose from 38 cm H_2O to 56 cm H_2O while the P_{plat} rose only to 38 cm H_2O. A chest radiograph revealed complete right lung collapse. Approximately 200 mL of thick, tenacious, green-brown sputum was aspirated from the right lung using fiberoptic bronchoscopy and saline lavage. The patient was positioned with his left side down, but 4 hours later P_{aO_2} had risen only to 54 mm Hg. After bronchoscopy, the intrinsic PEEP level increased from 4 cm H_2O to 10 cm H_2O above the set PEEP. A repeat chest radiograph showed a partially re-expanded right lung and a collapsed left upper lobe. Another bronchoscopy yielded copious thick yellow plugs.

As a result of this clinical deterioration, V_T was increased to 7 mL/kg (with P_{plat} remaining at 35 cm H_2O) and albuterol therapy (2.5 mg) was initiated and administered every 4 hours. In addition, intermittent PEEP was initiated to raise the applied PEEP level from 20 cm H_2O to 30 cm H_2O for 2 breaths every 3 minutes. During the intermittent PEEP breaths P_{plat} increased to 50 cm H_2O.

Twelve hours after the first bronchoscopy, P_{aO_2} had increased to 81 mm Hg on an F_{IO_2} of 0.65. By the next day (ARDS day 9), the P_{aO_2}/F_{IO_2} ratio had returned to 198 mm Hg and the LIP had decreased to 18 cm H_2O. The regimen of intermittent PEEP, V_T of 7.0 mL/kg, and albuterol therapy was continued over the next 10 days, with no further incidents of lung collapse. Unfortunately, 9 days following lung collapse, the patient developed multiple intra-abdominal abscesses, recurrent tissue necrosis, and candida sepsis. The patient died from multiorgan system failure 2 months after the incident of lung collapse.

Discussion

This case documents severe bronchial obstruction and multilobar collapse secondary to secretion retention in a complex case of ARDS. There were 3 potential contributions to the development of bronchial obstruction in this case: (1) inadequate humidification, (2) inadequate suctioning, and (3) lack of an appropriate lung inflation pattern.

During mechanical ventilation, tracheal mucus flow is maintained when the absolute humidity of inspired gases is 33 mg H_2O/L,[13] and is impaired when the relative humidity decreases to 50% at 37° C (22 mg H_2O/L).[14] Our patient's inspired gases were conditioned with an MR700 humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) with a heated wire circuit. The inspired gas exited the humidifier at 37° C, and the inspiratory limb was heated to 39° C[15] in order to offset the 1–3° C temperature drop that normally occurs across the endotracheal tube.[13] The mean (± standard deviation) airway temperature during the 12 days preceding and 9 days following bronchial obstruction was not different (38.8 ± 0.3° C and 38.4 ± 0.2° C, respectively, $p = 0.22$ by Wilcoxon signed-rank test). Given the consistent airway humidity and aggressive fluid resuscitation to treat the patient's hemorrhagic pancreatitis, we doubt there was a clinically important humidity deficit.

Prolonged exposure to high F_{IO_2} and narcotic use are known to depress mucus transport and increase retention of secretions, while treatment with β agonist may improve secretion clearance.[16] Over the entire 22 days, the patient required high levels of continuous narcotic infusion. Prior to bronchial obstruction, F_{IO_2} was seldom lower than 0.60, whereas after bronchial obstruction F_{IO_2} was generally less than 0.50. Therefore, the lower F_{IO_2} requirements and albuterol therapy may have facilitated bronchial hygiene during the post-bronchial-obstruction period.

Retained secretions during mechanical ventilation may occur when tracheobronchial suctioning is either infrequent or ineffective. The number of daily suctioning procedures preceding and following bronchial obstruction was not different (4.7 ± 1.1 and 4.9 ± 0.8, respectively, $p = 0.47$ by Wilcoxon signed-rank test) Both the amount and consistency of the sputum obtained during suctioning did not appear to differ before and after bronchial obstruction. In retrospect, this may appear to have been inadequate. However, suctioning a patient with ARDS on high levels of PEEP can cause atelectasis from aspiration of intrapulmonary air,[9,15] resulting in persistent hypoxemia.[9] This was a complication in our case, as suctioning often resulted in prolonged decreases in S_{pO_2}, despite the use of a closed tracheal suction system to minimize PEEP loss. Enhanced aspiration of intrapulmonary air during suctioning (because of excessive catheter size)[17] was not a factor, as our patient had an 8.0 mm internal-diameter oral endotracheal tube in place and was suctioned consistently with a 14 French (4.6 mm external diameter) tube.[18]

The combination of a very low V_T and a set PEEP below the LIP may have created an inappropriate lung inflation pattern that contributed to lung collapse. After bronchoscopy the patient was managed on a higher V_T, intermittent PEEP was added, and the applied PEEP exceeded the LIP. All three of these factors may have helped improve pulmonary hygiene. Positive expiratory pressure therapy and deep inspirations are believed to be necessary to build up sufficient positive pressure behind peripheral secretions and mucus plugs (through peripheral collateral channels)[19] to force secretions toward the central airways.[20] Although augmented V_T delivery has not been proven to enhance secretion removal during mechanical ventilation, the previous standard of using large V_T (12–15 mL/kg) may have obscured the issue.

Sigh maneuvers tend to be effective in extrapulmonary etiologies of ARDS because abnormal chest wall compliance and small airway closure are prominent features.[21] Pelosi et al[21] found that C_{RS} and end-expiratory lung volume improved after sigh breaths were added to low V_T ventilation, even when the applied PEEP was set above the LIP. Sighs can be delivered by intermittently raising the PEEP level and have been shown to increase end-expiratory lung volume and dynamic C_{RS}.[22] Sighs decrease airways resistance and therefore may counter small airway closure in ARDS.[21]

A case report cannot prove that low V_T ventilation causes lung collapse from retained secretions. However, our report suggests that extreme lung-protective ventilation (ie, $V_T < 5$ mL/kg) in ARDS may contribute to impaired pulmonary hygiene, particularly when ARDS is complicated by the abdominal compartment syndrome. We believe that using lung-protective ventilation in ARDS is crucial, as the National Institutes of Health ARDS Network study[23] has found a 22% reduction in mortality with this strategy. However, the potential risk of persistent atelectasis and retained secretions during lung-protective ventilation should increase awareness regarding the adequacy of pulmonary hygiene and incorporating adjunctive treatments to improve secretion clearance.

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Pneumonitis after Intravenous Self-Administration of Solvent

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Intravenous self-administration of petroleum distillates is a rare condition. Most experience with petroleum distillates poisoning is with ingestion by children, and the most common and serious manifestation is chemical pneumonitis. We report a case of chemical pneumonitis after intravenous self-administration of ink solvent. [Respir Care 2001;46(1):53–55] *Key words: pneumonitis, intravenous self-administration, ink solvent, petroleum distillates, poisoning.*

Introduction

Intravenous self-administration of petroleum distillates is a rare condition. Most experiences with petroleum distillates poisoning is with ingestion by children,[1–3] and the most common and serious manifestation is chemical pneumonitis.[1,2,4–7] However, experiments have shown that intratracheal administration increases pulmonary damage and intravenous administration produces similar changes.[3,8–11] We report a case of chemical pneumonitis after intravenous self-administration of ink solvent.

Case Summary

A 39-year-old man with a history of alcohol and drug abuse (intravenous cocaine), intravenously injected 6 mL of an ink solvent called Angio3000 (a compound of alcohol, ester, ketone, glycol, and aromatic hydrocarbon, made in São Paulo, Brazil) 2 hours before admission. On admission he was afebrile and presented with severe dyspnea, sweats, perioral cyanosis, blood pressure 110/60 mm Hg, heart rate 100 breaths/min, respiratory rate 60 breaths/min, and diffuse inspiratory crackles on auscultation. The neurologic examination disclosed no focal signs. The pupils were equal and reactive, and the plantar response was normal. One hour after admission, a chest radiograph showed diffuse bilateral patchy opacities in the lungs (Fig. 1). Arterial blood gas analysis (on room air) showed pH 7.33, partial pressure of oxygen 36 mm Hg, partial pressure of carbon dioxide 33 mm Hg, HCO_3 17 mMol/L, and arterial oxygen saturation 64%. The dyspnea worsened progressively, he was admitted to the intensive care unit, and mechanical ventilation was instituted with positive end-expiratory pressure of 10 cm H_2O and fraction of inspired oxygen 0.50. He was treated with intravenous methylprednisolone (500 mg bolus, then 125 mg every 4 hours) and with intravenous cotrimoxazole (180 mg every 8 hours).

Complete blood count, liver function tests, and serum levels of urea nitrogen, creatinine, calcium, and phosphorus were unremarkable. The heart and respiratory rate returned to normal within 3 days. By day 14, the patient was weaned from the ventilator with normal blood gases and without complaints. A chest radiograph (Fig. 2) showed improvement of the infiltrates in the perihilar regions, and fiberoptic bronchoscopy disclosed a bronchial tree with erythematous mucosa and purulent material in the upper airways. Specimens were negative for bacteria, mycobacteria, and fungi by stains and culture. Material from a bronchial washing showed reactive respiratory epithelial cells and alveolar macrophages. The patient was discharged asymptomatic. Pulmonary function tests performed a month later showed normal results. Over a one-year period of follow-up, the patient showed no clinical or laboratory abnormalities and chest radiographs showed no changes. The patient is in psychiatric treatment for alcohol and drug abuse.

Discussion

Angio3000 is a petroleum distillate. It is compound of alcohol, ester, ketone, glycol, and predominantly aromatic hydrocarbon. Intravenous administration of petroleum distillates is a rare cause of chemical pneumonitis, which can

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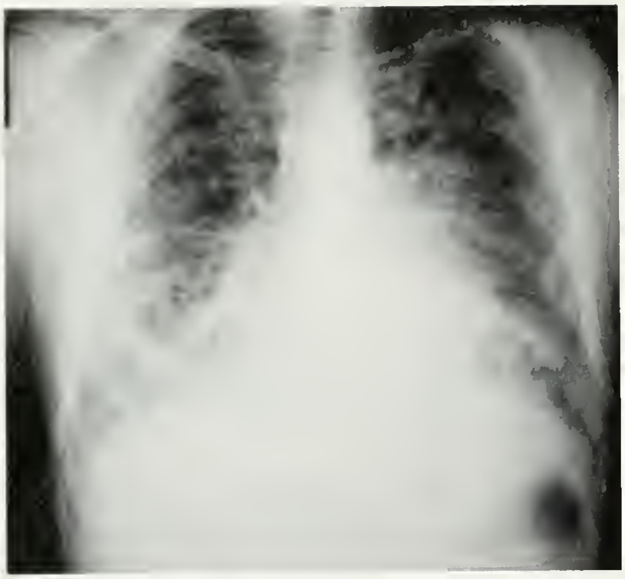

Fig. 1. Chest radiograph 3 hours after intravenous administration of ink solvent shows diffuse patchy infiltrates in the lungs.

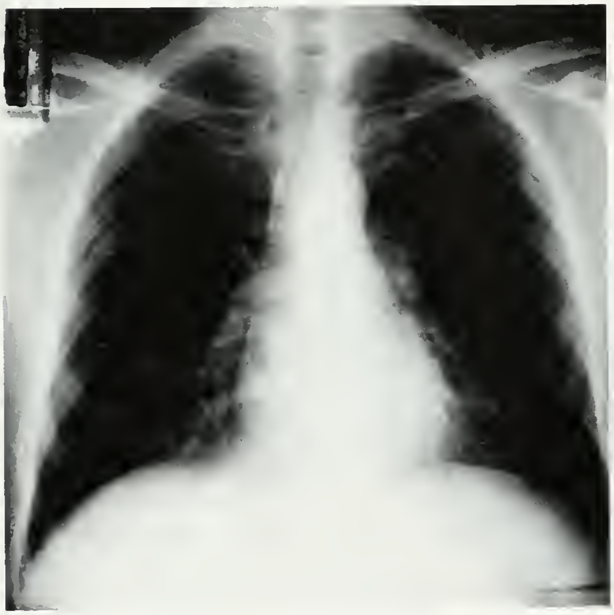

Fig. 2. Chest radiograph after 14 days shows improvement of the infiltrates.

be differentiated from hydrocarbon ingestion on pathogenic, clinical, and radiologic bases.[10]

Most patients who ingest petroleum distillates exhibit pulmonary abnormalities such as pulmonary edema or chemical pneumonitis,[5,12] and half of those patients develop respiratory symptoms.[5,12–15] Those patients are symptomatic for approximately a week[5,6,12,16] and usually develop moderate pulmonary infiltrates that are most prominent in the medial and lower portions of the lung. Perihilar regions are also commonly involved.[6,17–19] Pneumothorax, pneumomediastinum, subcutaneous emphysema, pleural effusion, and pneumatoceles may also occur.[14,19,20]

Pulmonary damage after intravenous administration of petroleum distillates results from hematogenous carriage and seems to be caused by a direct action of the hydrocarbon on the lung, causing changes in the surface tensions.[9,10,21] Pulmonary symptoms are more prominent in intravenous administration than in ingestion of petroleum distillates. The distribution of the lesions after experimental intravenous injection of hydrocarbon compounds was uniform through both lungs. This contrasts with the pulmonary lesions found in cases of petroleum distillate ingestion, which remain localized. It seems to suggest that the lesions caused by ingestion are more from aspiration than from gastrointestinal absorption.[9]

Despite blood gas analyses, this report was similar to experimental study of intratracheal administration of kerosene, which reduced the arterial partial pressure of oxygen levels substantially during the first 18 hours while arterial partial pressure of carbon dioxide remained normal. These abnormalities indicate that the respiratory symptoms are due to ventilation-perfusion abnormalities.[10,22] In our case, the hypocapnia and severe hypoxemia reflected the tachypnea, the increased cardiac output, and the reduced total vital capacity.

Experimental studies failed to determine if corticosteroid therapy could prevent the development of fibrosis and avoid pulmonary hemorrhage or edema.[2,3,13,23] Our case demonstrates a patient who presented with acute pulmonary failure caused by chemical pneumonitis after intravenous administration of hydrocarbon. Although there is not a known or accepted treatment for pneumonitis related to intravenous solvent exposure, in this case there was clinical resolution with prophylactic antibiotic, corticoid, and conservative supportive measures. The efficacy of these methods remains unclear.

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2000 Donald F Egan Scientific Lecture

Are Respiratory Therapists Effective? Assessing the Evidence

James K Stoller MD

In the current cost-attentive health care climate, the effectiveness of various providers in delivering care is being examined closely. To evaluate the effectiveness of respiratory therapists (RTs) in delivering respiratory care in the intensive care unit (ICU), in adult non-ICU inpatient care, and in ambulatory care, this 27th Egan Lecture presents a systematic review of the available literature examining RTs' effectiveness in these settings. Overall, available studies support the effectiveness of RTs in providing care in various roles in all clinical venues, with the strongest evidence based on the results of concordant randomized controlled clinical trials. Indeed, 5 randomized clinical trials show that RTs are effective in implementing respiratory care protocols to wean patients from mechanical ventilation and in appropriately allocating respiratory care services to adult non-ICU inpatients. Lower levels of evidence support RTs' roles in performing intubation, placing indwelling arterial lines, performing mini-bronchoalveolar lavage, allocating arterial blood gases, and in various counseling and teaching roles. Notwithstanding the considerable body of available evidence that buttresses RTs' effectiveness in delivering care, additional rigorously designed studies are needed to examine RTs' effectiveness in new roles (eg, geriatric care, pediatric care), in new venues (eg, extended care facilities), and to assure the generalizability of available findings to the broad spectrum of health care facilities (eg, academic and community-based facilities alike). Finally, the respiratory therapy community must continue to cultivate and suppport investigative expertise to assure continued inquiry. [Respir Care 2001;46(1):56–66] *Key words: respiratory therapists, effectiveness, intensive care unit, protocol, allocation.*

Introduction

I am humbled by the honor of presenting the 27th Donald F Egan Lecture. As one of the first physician champions of respiratory care, Dr Egan clearly recognized the importance of respiratory care to the well-being of our patients. In writing the first major textbook of respiratory care in 1969,[1] a work to which I have since been privileged to contribute, Dr Egan had a vision of optimal respiratory care. Like all of you here whose practice has been shaped by Dr Egan's contributions, I share this vision. In this spirit, my purpose in today's lecture is to critically examine the evidence regarding how effective respiratory therapists (RTs) are and how much you contribute to clinical care. More specifically, in the parlance of our current cost-attentive health care environment, I want to consider what is the "value added" of RTs? That is, what do you do that is better than anyone else and for which you are therefore essential to health care?

In examining the evidence regarding RTs' effectiveness as health care providers, I want to begin by defining effectiveness,[2] which is simply the impact of an intervention (eg, a treatment, a diagnostic test) under actual conditions of use in the community or "real world." In talking about the effectiveness of RTs, I refer to your impact in everyday practice, not only under the unique or special circumstances of a study. Thus, a confident conclusion that RTs are effective requires concordant results from at least several well-designed and generalizable studies.

Measurements of effectiveness are of 2 types:

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Table 1 Grades of Evidence for Rating Quality of Study Design

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

*The grades are those of the United States Preventive Services Task Force.[4]

1. Process measures, which examine the way RTs execute tasks (eg, procedural skills such as placing indwelling arterial catheters, fund of knowledge, etc), and

2. Outcome measures, which evaluate the clinical results of RTs' care (eg, survival rates, appropriateness of care, length of hospital stay, etc).

Having defined the types of measures that will be discussed, I will begin by presenting Dr Egan's 1969 observations about the roles and possibilities of respiratory care. Next, using techniques borrowed from evidence-based medicine systematic reviews and meta-analysis,[3] I will cite and summarize the studies that, in my view, have best assessed RTs' effectiveness. I will then evaluate and rate the quality of these best currently available studies, which will be categorized in 3 clinical venues: the intensive care unit (ICU), non-ICU adult inpatient care, and ambulatory care. Corollary questions include: In what clinical activities have RTs been assessed and to whom have they been compared? Does this evidence support a conclusion that RTs are effective? To the extent that definitive answers are not available, what additional research is needed?

For rating the available literature, I shall adopt the 5-category rating system for grades of evidence developed by the United States Preventive Services Task Force (Table 1).[4] Finally, recognizing my being an internist and pediatrically naïve, I will limit my discussion to evidence regarding adult care.

An Early View of Quality Respiratory Care: Dr Egan's Views on the Role of Respiratory Therapists

In the context of this Egan Lecture, it is fitting to begin by reviewing Dr Egan's vision of effective respiratory care and the role of RTs. Indeed, as Dr Egan's following remarks show, he recognized 4 essential themes that have set the direction for respiratory care over the last 3 decades and that form the underpinnings of RTs' role in current health care. These themes are:

1. There is a need for highly skilled providers with respiratory expertise.

2. Effective RTs will have knowledge and skills different from and complementary to those of all other providers, including physicians.

3. The effectiveness of RTs will assure high acceptance, though there is the potential for overlap and/or blurring of roles with other providers.

4. There is a strong need for close collaboration with other health care providers.

With this overview in mind, Dr Egan's own words in the first edition of "Fundamentals of Inhalation Therapy" in 1969[1] cogently articulate the mission and goals of respiratory care:

> Hospitals have been facing an increasing load of patients with cardiopulmonary diseases over the past several years but are often lacking both the physical facilities and technical personnel to provide modern care. . . The techniques that have evolved for the treatment of these patients require the assistance of skilled technical help, and we have already indicated that they are too detailed for the average attending physician, house physician, or nurse to supervise or administer. It was in response to this need that the technical specialty of inhalation therapy emerged to take its place in the hospital organization. Historically, the predecessor of inhalation therapy was the well-known but little regarded hospital oxygen service. However, the highly skilled offspring bears little resemblance to its humble ancestor, for during his evolution, the inhalation therapist has undergone intensive medically supervised education and training, enabling him/her to provide skills and services not available from any existing hospital personnel. . .
>
> Finally, we might indulge in some imaginative speculation as to what the future could hold for inhalation therapy. The rapidly increasing population is straining the ability of currently organized medicine to supply adequate medical care. The problem is not merely a quantitative shortage of personnel; but with the emergence of so many new diagnostic and therapeutic techniques, skills are needed that have not traditionally been part of medicine. This is an era of technical as well as professional specialization, and it seems almost inevitable that delivery of medical care to our society in the near future will depend upon the delegation of many responsibilities to highly skilled and finely trained nonphysician specialists. One of the fastest-growing segments of medicine is that of cardiopulmonary disease, and it is in

Table 2 Ratings of Evidence Regarding Respiratory Therapists' Effectiveness in the ICU*

Clinical Activity	Evidence Rating
Performing intubation	II-2
Placing indwelling arterial lines	III
Performing mini-bronchoalveolar lavage	III
Allocating arterial blood gases	II-3
Weaning patients from mechanical ventilation using respiratory care protocols	I

ICU = intensive care unit

*Based on United States Preventive Services Task Force Grades of Evidence scheme (see Table 1)[4]

> this area that the present inhalation therapist may find herself becoming a more committed part of the team. With his/her background in cardiopulmonary physiology, his/her participation in laboratory diagnosis, and his/her intimate patient-care experience, (s)he is a natural subject to expand into related cardiovascular fields, where technology is becoming increasingly important.

With those prescient words in mind, let us examine the current literature regarding the role of RTs, considering first the ICU, then non-ICU adult inpatient care, and finally ambulatory care.

Are Respiratory Therapists Effective in the Intensive Care Unit?

Studies examining the effectiveness of RTs in the ICU have considered both process measures (eg, RTs' success in performing intubation,[5-9] in placing indwelling arterial lines,[10] and in performing mini-bronchoalveolar lavage [BAL][11]) and clinical outcome measures (eg, in determining the appropriateness of drawing samples for arterial blood gas [ABG] analysis[12] and in weaning patients from mechanical ventilation[13–15]). Table 2 rates the evidence from available studies using the United States Preventive Services Task Force[4] grades of evidence scheme.

Table 3 summarizes 4 studies of RTs' effectiveness in performing intubation.[5-8] Indeed, RTs' role as endotracheal intubators was foreseen by Ahlgren et al[9] in 1966:

> Included in the training (of RTs) is practice in inserting an endotracheal tube efficiently and atraumatically. Training of this type must be under the direction of a physician, preferably an anesthesiologist. . . . After 2 or 3 months of actual observation and participation in resuscitation endeavors, a therapy technician is able to cope with them independently, needing the anesthesiologist only as a consultant.

In the earliest of the 4 studies evaluating RTs' effectiveness in performing intubation, Connelly and Smith[5] described experience at a community hospital in which the impetus for RTs to provide intubation services was the scarcity of qualified physicians. In a series of 143 consecutive intubations over one year, RTs provided 52% of the intubations, with a moderate complication rate (16%) that was similar to other providers in that series.

In another study also conducted in 1981, McLaughlin and Scott[6] reported that establishment of a respiratory therapy intubation service was encouraged by the hospital's anesthesiologists. RTs underwent training, first using mannequins, and then under anesthesiologists' supervision, in the operating room and on the hospital wards. In this reported experience of 50 consecutive emergency intubations over 20 weeks at Wilmington Medical Center, the intubation success rate was 100%. Seventy percent of intubations were successful on the first pass, and the mean number of intubation passes to success was 1.78. The required time for intubation was less than 1 minute in 78% of patients.

In the largest available series, Thalman et al[7] described their experience with an RT intubation service at Duke University Medical Center. As in the series by McLaughlin and Scott,[6] RTs underwent multifaceted training, including 8 hours of didactic training, written and practical examinations, performance of 10 supervised intubations, advanced cardiac life support certification, and skills maintenance by ongoing performance of a large number of intubations. After a longstanding experience with this service, the authors presented the intubation outcomes of 833 individuals who needed intubation between July 1990 and June 1991. During that period, RTs successfully intubated 94.9% of patients. Of the remaining 42 patients, 39 were

Table 3. Intubation Success Rates by Respiratory Therapists: Summary of Available Series

Author (Date)	*n* Patients	% Successful	% Complications
Connelly and Smith (1981)[5]	143	96	16 (including 3 unsuccessful attempts)
McLaughlin and Scott (1981)[6]	50	100 (70% on first attempt)	0
Thalman et al (1983)[7]	833	95	11.5 (all minor)
Zyla and Carlson (1994)[8]	178	90 (backup service provided)	1.6 (none severe)

subsequently intubated by physicians, and 3 required tracheotomy.

In the most recent available report, by Zyla and Carlson,[8] development of an RT backup intubation service was prompted by a desire to avert anesthesiologists' being summoned away from the operating room. After initial training in didactic sessions, mannequin intubations, and 15 supervised intubations in the operating room, RTs were asked to provide backup to house officers. In the experience of 178 requests for intubation over 49 months, RTs successfully performed intubation in 90% of instances. Complications (eg, esophageal intubation) occurred in 1.6% and were quickly recognized and corrected.

Taken together (see Table 3), this collected observational experience suggests that with appropriate training and supervision, RTs can provide intubation services effectively. Because RTs' effectiveness as intubators has not been compared to other health care providers in a randomized controlled trial, this literature bears an evidence grade of II-2 (see Tables 1 and 2). As with many aspects of respiratory care practice and as an emerging theme in this systematic review of RTs' effectiveness, the paucity of definitive studies leaves gaps in current understanding. Because controversy can thrive in a vacuum of data, this lack of studies serves as a challenge to the respiratory care community to organize and conduct rigorous new research to clarify this and other remaining uncertainties.

Other ICU roles in which RTs' process effectiveness has been examined include placing indwelling arterial catheters[10] and performing mini-BAL.[11] Examining RTs' effectiveness in placing indwelling arterial catheters, Rowley et al[10] provided RT training consisting of written didactic materials and direct observation by an anesthesiologist while each RT placed at least 3 catheters. In that series, 12 RTs performed 119 intra-arterial catheter attempts, with 97% success and without intermediate or late complications.

Also, Kollef et al[11] assessed RTs in performing mini-BAL, which involves passing telescoping plugged catheters through the endotracheal tube to obtain lavage specimens. As performed by RTs, mini-BAL was well-tolerated and carried a low complication rate, similar to that observed with conventional bronchoscopy performed by physicians.

In summary, as presented in Table 2, the literature regarding placing indwelling arterial lines and performing mini-BAL bears an evidence grade of II-3 to III. Overall, it can be concluded that available studies do favor RTs' effectiveness in several different process measures in the ICU, but that more studies are needed, and randomized controlled trials are encouraged.

Beyond process measures, outcome studies examining RTs' effectiveness in the ICU have considered their role in using protocols to optimize the ordering of ABGs[12] and RTs' effectiveness in weaning patients from mechanical ventilation.[13-15] Indeed, as is evident in many of the studies that have examined RTs' effectiveness in achieving clinical benefits, protocols have been widely implemented as a strategy to optimize and to standardize the care RTs provide.[16,17] Although published concepts of protocols vary, I would offer the following definition of a respiratory care protocol: A protocol is a structured approach for analyzing a clinical situation with nested treatment decisions that are intended to assure optimal respiratory care. To the extent that optimal therapy is defined by consensus statements or evidence-based analyses, protocols attempt to operationalize such best practices. At the same time, protocols must be distinguished from inviolate rules because protocols encourage critical thinking and invite protocol exception where clinical circumstances fall outside the proposed algorithms. Thus, protocols ideally blend rigorous uniformity with critical thinking and, where appropriate, exception. With this concept of protocols in mind, we can further consider the available evidence regarding RTs' effectiveness in the ICU.

In an early but especially noteworthy study regarding RTs' effectiveness in determining when to sample for ABG analysis in ICU patients, Browning et al[12] assessed the appropriateness of ABGs sampled during 3 intervals: before a protocol for ABG sampling was implemented, and then 1 and 3 months after implementation. Implementation of a protocol was associated with improved allocation of ABGs: the rate of inappropriately ordered ABGs declined from 43% before implementing the protocol to 33% 1 month after implementation to 31% 3 months after implementation. Most strikingly, when the investigators assessed the rate of inappropriate orders by the type of provider ordering the sample, RTs performed best. Specifically, RTs' rates of inappropriately ordered ABGs were 3% after 1 month of protocol use and 15% after 3 months, whereas the respective rates for other providers were strikingly higher: 45% after 1 month and 37% after 3 months.

Subsequent studies[18,19] have confirmed the value of protocols drafted by a multidisciplinary ICU group in improving the allocation of ABGs in the ICU and in directing the placement of indwelling arterial catheters. For example, Pilon et al[18] conducted an observational cohort study in which the rate of appropriate ABGs increased from 44% at baseline to 78–79% at 2 to 13 months after implementing a protocol drafted with multidisciplinary (including respiratory care) consensus. Other benefits associated with the ABG protocol included a decrease in the mean number of ABGs per patient per day (from 4.9 to 2.4–3.1, $p < 0.001$) and a concomitant cost savings of $19.18 (Canadian) per patient per day, with no identifiable adverse effects on outcome.

Studying the impact of a protocol addressing when to place indwelling arterial catheters, Ozgun et al[19] reported

Table 4. Summary of Available Randomized Trials Regarding the Effectiveness of Respiratory Therapists

Clinical Activity	Author	Date	*n* Patients	Findings
Weaning from mechanical ventilation	Kollef et al[13]	1997	357	Use of protocols was associated with shorter duration of mechanical ventilation.
	Ely et al[14]	1996	300	Routine daily trials of spontaneous breathing was associated with shorter duration of mechanical ventilation.
	Marelich et al[15]	2000	253	Use of protocols shortened duration of mechanical ventilation.
Respiratory care protocol service	Stoller et al[17]	1998	145	Use of respiratory therapy consult service was associated with improved allocation of respiratory care service, with lower costs, and with no adverse events.
	Kollef et al[20]	2000	694	Use of respiratory protocol service was associated with lower charges and fewer orders discordant with guidelines.

that implementing the protocol was associated with a lowered rate of catheter placement (from 29.3% of ICU patients before to 13.7% after the protocol) and a trend toward fewer ABGs per patient (from 7.0 to 5.6, $p = 0.9$). Again, these benefits were achieved without adverse effects (eg, on ICU length of stay, ICU survival rate, or hospital survival rate).

Finally, the most compelling current evidence regarding RTs' effectiveness in the ICU consists of 3 randomized controlled trials examining RTs' performance in weaning patients from mechanical ventilation using protocol guidance (Table 4).[13-15,17,20] In the first of these trials, Kollef et al[13] allocated 357 patients in 4 ICUs to receive physician-directed versus protocol-directed weaning. Benefits of protocol use included a significantly shortened duration of mechanical ventilation (mean 69 h vs 102 h, $p = 0.029$) and a trend toward lower costs (by $42,960). No adverse effects were observed.

In a more recent randomized controlled trial, Ely et al[14] assessed the outcomes of mechanically ventilated patients who were weaned under usual physician-directed care versus those undergoing daily assessments of weanability and, if deemed suitable, a standard trial of spontaneous breathing administered by RTs. As in the earlier trial,[13] use of protocols conferred benefits. Specifically, daily assessment of weanability by therapists with subsequent therapist-directed weaning on physician approval was associated with a shortening of weaning time by a median of 2 days ($p < 0.001$) and of total mechanical ventilation by 1.5 days ($p < 0.003$).

Most recently, Marelich et al[15] compared outcomes from protocol-based weaning by RTs and nurses versus usual physician-directed weaning in a third randomized controlled trial. The protocols were generated with multidisciplinary input in the usual course of ICU planning, and no special meetings or measures were reportedly needed. In the group allocated to protocol-based weaning ($n = 129$ patients), therapists and nurses assessed patients' candidacy for spontaneous breathing trials, conducted and assessed the outcomes of such spontaneous breathing trials, and then recommended to the physician discontinuation from mechanical ventilation if the patient succeeded in a 30-minute spontaneous breathing trial. In the group managed by physician-directed weaning ($n = 124$), weaning assessments and orders were implemented only on explicit physician orders. As in the 2 earlier trials, the study results showed significant benefits of protocol-based weaning, including:

1. A shorter duration of mechanical ventilation (median 68 h vs 124 h [$p = 0.0001$], risk ratio favoring protocols 1.67 [$p = 0.009$] after correction for acute physiology and chronic health evaluation scores, age, duration of respiratory failure before weaning, and diagnosis),
2. A shorter interval between achieving criteria for discontinuation of ventilation and actual discontinuation ($p = 0.006$), and
3. A shorter interval between starting mechanical ventilation and meeting discontinuation criteria (median 42 h vs 79 h, $p = 0.0001$).

These benefits were achieved without any significant detrimental effects; specifically, no significant differences in rates of failure of discontinuation of mechanical ventilation or hospital mortality were observed.

Taken together, this evidence supporting RTs' effectiveness in weaning patients from mechanical ventilation is the strongest among the studies evaluating RTs' roles in intensive care. Specifically, by virtue of the concordant results from 3 randomized, controlled clinical trials (see Tables 2 and 4), an evidence grade of I is warranted.

Overall, the following conclusions regarding RTs' effectiveness in the ICU can be offered:

1. Available studies demonstrate that RTs are effective in various roles in the ICU, including conducting weaning from mechanical ventilation, ordering ABGs, and placing indwelling arterial lines.
2. The available evidence is strongest (ie, with concordant randomized controlled trials) for RTs' role in implementing protocols to wean patients from mechanical ventilation.

Table 5. Ratings of Evidence Regarding Respiratory Therapists' Effectiveness in Non-ICU Adult Inpatient Care*

Clinical Activity	Evidence Rating
Individual respiratory care modalities	II-2
Titrating oxygen	
Administering bronchopulmonary hygiene	
Generating an appropriate overall respiratory care plan guided by respiratory care protocols	I

ICU = intensive care unit

*Based on United States Preventive Services Task Force Grades of Evidence scheme (see Table 1)[4]

3. Observational studies also support RTs' effectiveness and, in some instances, favor their performance compared with other providers of ICU care.
4. Remaining uncertainty about RTs' effectiveness reflects the paucity of available studies and underscores the need for additional well-designed, randomized, controlled trials.

Are Respiratory Therapists Effective in Providing Non-Intensive Care Unit Adult Inpatient Care?

RTs' effectiveness in providing non-ICU adult inpatient care has been evaluated in observational studies for several specific therapies (eg, oxygen administration, titration,[21,22] and bronchopulmonary hygiene[23,24]) and, in both observational studies[25–28] and randomized trials,[29,30] for the overall appropriate allocation of respiratory care services in the context of protocol-guided therapy. Table 5 presents the evidence grades of studies that examine RTs' effectiveness in providing non-ICU inpatient respiratory care. The discussion that follows presents examples of observational studies regarding single modalities of therapy and protocol services, and will focus on randomized trials that assess RTs' effectiveness in implementing protocol programs.

As an example of an observational study evaluating RTs' effectiveness in administering a single respiratory care modality, Komara and Stoller[21] evaluated the impact of an RT-administered protocol for titrating supplemental oxygen in postoperative patients. In comparing the duration and cost of supplemental oxygen use in a convenience sample of 20 postoperative patients whose oxygen was titrated by RTs according to protocol versus 20 patients whose oxygen was managed by their physicians, several benefits of protocol-based care by RTs were observed. Specifically, the duration of postoperative oxygen used to achieve a room air arterial oxygen saturation $\geq 92\%$ (measured via pulse oximetry) was shorter (mean 2.1 ± 0.64 d vs 3.45 ± 1.28 d, $p < 0.003$), the associated real costs of administering oxygen (eg, RTs' time, cannula, oximeter depreciation, etc) were lower (mean total savings of \$389.52, $p < 0.003$), and there were no adverse effects observed. The results support RTs' effectiveness as implementors of an oxygen titration protocol to enhance the allocation of respiratory care services.

In an observational study of an oxygen protocol in a community hospital, Konschak et al[22] reported similar benefits of decreased oxygen utilization after the protocol was implemented. Specifically, for patients on a single hospital ward, protocol use was associated with a shorter duration of unneeded oxygen, (by 3.87 days p, < 0.05), less wasted oxygen per patient (by 15,294 L, $p < 0.05$), and lower cost per patient of oxygen used when no longer needed (by \$4.47 per patient, for a total hospital savings of \$7,915 per year).

In another example of an observational study suggesting RTs' effectiveness as allocators of specific respiratory treatments, Shapiro et al[23] assessed patterns of utilizing bronchial hygiene therapy before and after implementing protocols that were overseen by the medical director. The results show that introducing protocols was associated with a 61% reduction of bronchial hygiene therapy outside of the ICU, with a concomitant savings of more than \$250,000 and no attributable adverse effects. Specifically, though the volume of therapies decreased from 60,713 to 23,594, overall hospital mortality over the compared interval (1983–1986) did not change and "no valid instance of increased patient morbidity attributable to differences in bronchial hygiene therapy was brought to the attention of the medical director."[23]

In a later randomized trial examining the impact of physician review of bronchial hygiene orders, Alexander et al[24] observed a similar reduction (by 52%) in bronchial hygiene orders that fell outside of protocol indications. Specifically, 101 patients ordered to receive unindicated chest physiotherapy were randomly allocated to a group of patients who received the ordered therapy ($n = 54$) and a group of patients for which the pulmonary fellow called the ordering physician regarding the orders ($n = 47$). The intervention group underwent 45% fewer chest physiotherapy treatments than the control group, with concomitant savings of at least \$176,000, and no change in mortality or hospital length of stay. Like the results of earlier studies,[23] these findings suggest that a protocol-based intervention to interdict inappropriate respiratory care orders can improve allocation. Although physicians-in-training provided the intervention in this study, experience in other studies suggests that RTs can also be highly effective in this role.[10,12,23]

Beyond these studies regarding single respiratory care modalities, early observational studies suggested that protocols could decrease misallocation of respiratory care services overall while preserving clinical benefit. For example, in a pioneering 1981 report, Nielsen-Tietsort et al[25] espoused "a new therapy delivery system—The Respiratory Care Protocol" at the Lutheran Medical Center in Wheat Ridge, Colorado. In 1986, Zibrak et al[26] reported the results of a historical control study in which implementation of guidelines by RTs was associated with marked reductions in all categories of respiratory therapy (by 55–92%) with no change in hospital morbidity and/or mortality from pulmonary disorders. In the subset of patients undergoing coronary artery revascularization, protocol use was associated with a decrease in the mean hospital length of stay (by 5.0 days) and in the rate of pulmonary complications (from 16.7% to 5.5%).

In a more recent report, Kirby and Durbin[27] conducted an observational cohort study to evaluate the impact of a respiratory therapy assessment and treatment team on patient readmission to the ICU. Comparison of the intervention cohort managed by the assessment-treatment team (1992–1993, $n = 69$ evaluable patients) with the control cohort before the team was implemented (1988–1989, $n = 82$ patients) showed a significantly lower hospital mortality rate in the intervention group (13% vs 47%, $p < 0.0001$). Although the observational design precludes firmly ascribing the decreased mortality rate to the team alone, these results suggest that the assessment-treatment team conferred benefit and agree with earlier findings from this group[12,28] and others.[29] In summary, these and other observational studies[28,29] support RTs' effectiveness in determining non-ICU adult inpatient respiratory care.

However, the strongest evidence supporting RTs' effectiveness in providing non-ICU inpatient respiratory care comes from 2 randomized, controlled trials that compared the impact of inpatient respiratory care protocol services with usual physician-directed care. Both trials found that in the context of a protocol service, RT-directed care allows better allocation of respiratory care services than physician-directed care (see Table 4).

In the first of these 2 trials, Stoller et al[30] reported a randomized controlled trial in which 145 adult non-ICU inpatients at The Cleveland Clinic Hospital were randomly allocated to receive respiratory care orders as placed by the managing physicians or to have their physicians' respiratory care orders preempted by those generated by an RT applying protocols. The protocols, which have the format of branched logic diagrams, were developed to operationalize American Association for Respiratory Care Clinical Practice Guidelines for the modalities used. Compared with physician-directed care, the use of respiratory care protocols conferred several advantages, including achieving a higher rate of concordance with a gold standard respiratory care plan (82% vs 64%, using stringent agreement criteria, $p < 0.001$), and a trend toward lower true median respiratory care costs per patient ($130 vs $152, $p = 0.51$).

More recently, Kollef et al[20] reported similar findings in another randomized trial of respiratory care protocols at Barnes Hospital. In that study, 694 patients were allocated to one of 3 hospital firms according to their primary physicians' ward assignments. Unassigned patients were randomly allocated among the firms. In Firm A (but not in Firm B or C), the respiratory care plans were allocated by RTs using explicit protocols. In contrast, in Firms B and C, respiratory care orders were written by the managing physicians. Comparison of outcomes in Firms A, B, and C showed that use of protocols was associated with fewer respiratory therapy treatments (10.7 in Firm A vs 12.4 in Firm B vs 12.3 in Firm C, $p = 0.009$); a greater percentage of bronchodilators administered as metered-dose inhalers (89% in Firm A vs 77% in Firm B vs 78% in Firm C, $p = 0.01$); fewer respiratory therapy orders that were discordant with the protocol standard (24% in Firm A vs 58% in Firms B and C, risk ratio 0.42, 95% confidence interval 0.33–0.53); and lower respiratory care charges (mean $868 in Firm A vs $1,124 in Firm B vs $1,054 in Firm C, $p < 0.001$). As in the earlier randomized trial,[30] these benefits were achieved without adverse impact.

Taken together, these 2 randomized controlled trials (see Table 4) and earlier observational studies[26–29] demonstrate that RTs implementing protocol-based care can effectively allocate respiratory care services and that such protocol services improve allocation and lower costs, compared with traditional physician-directed respiratory care. As with the studies assessing RTs' effectiveness in weaning patients from mechanical ventilation,[13–15] these concordant randomized controlled clinical trials warrant an evidence grade of I (see Table 5).

Are Respiratory Therapists Effective in the Ambulatory Setting?

Finally, although ambulatory care has been the least studied clinical venue, several observational studies have addressed RTs' effectiveness in this setting. Specifically, RTs' effectiveness has been evaluated regarding inhaler device expertise,[31–33] their disposition to counsel patients on health maintenance,[34] their role as smoking cessation counselors,[35] and their impact in teaching medical students how to sample arterial blood.[36]

Three observational studies[31–33] have compared RTs with nurses and physicians on knowledge of and ability to use inhaler devices (Table 6). In the earliest of these, Guidry et al[31] evaluated 14 registered nurses, 12 certified respiratory therapy technicians, and 35 physicians (23 internal medicine residents at all 3 training levels [intern, junior, and senior resident], and 12 nonpulmonary faculty members) regarding their knowledge of metered-dose inhaler use and the correctness of their inhalation technique. The RTs demonstrated the best technique, with 92% performing at least

Table 6. Comparison of Respiratory Therapists and Other Medical Personnel in Use of Inhaler Devices

Author (Date)	*n*	RT (%)	RN (%)	Physician (%)	Comment
Hanania et al (1994)[33]	30 physicians 30 RNs 30 RTs	85	57	49	RTs significantly better physicians were trainees.
Guidry et al (1992)[31]	35 physicians (23 IM trainees, 12 IM faculty) 14 RNs 12 CRTTs	92 (≥ 4/7 steps)	57	65 house staff 57 non-pulmonary faculty	RTs also had higher knowledge scores
Interiano and Guntupalli* (1993)[32]	100 physicians 50 nurses 20 RTs	85	4	43 IM residents	Pulmonary fellows rated 100% good

RT = respiratory therapist
RN = registered nurse
IM = internal medicine
*Percentage rated "good" on metered-dose inhaler technique.

4 of the 7 steps correctly, versus 57% of nurses, 65% of house staff physicians, and 57% of nonpulmonary faculty ($p < 0.05$). RTs also demonstrated better knowledge than others on two of the 6 questions (regarding shaking the inhaler, inhaling, and expiration) but similar knowledge on the other 4 questions.

Interiano and Guntupalli[32] evaluated the proficiency of physicians ($n = 100$ internal medicine house staff and 6 pulmonary fellows), nurses ($n = 50$), and RTs ($n = 20$) in using metered-dose inhalers. Pulmonary fellows performed best, with all six achieving a rating of "good" (ie, ≥ 5 of 6 steps performed correctly). Among the remaining groups, RTs performed better than house officers or nurses (85% good vs 43% vs 4%, $p \leq 0.009$). Commenting on the "value added" of RTs in this context, the authors noted, "this study also suggests that RTs should be used more extensively in the current education of the patients with asthma, even in the outpatient setting."[32]

Most recently, Hanania et al[33] compared RTs, registered nurses, and internal medicine physicians-in-training regarding knowledge of and ability to use 3 inhaler devices: metered-dose inhaler, Turbuhaler, and Aerochamber. As in the earlier studies,[31,32] RTs had significantly higher scores on knowledge (67% for RTs vs 39% for nurses vs 48% for physicians, $p < 0.001$) and on the ability to use the devices (85% for RTs vs 57% for nurses vs 49% for physicians, $p < 0.001$).

Table 7. Ratings of Evidence Regarding Respiratory Therapists' Effectiveness in Ambulatory Care

Clinical Activity	Evidence Rating
Knowledge of and patients instruction regarding metered-dose inhalers	II-2
Health promotion counseling	III
Smoking cessation counseling	III
Educating medical students in arterial blood sampling	III

ICU = intensive care unit
*Based on United States Preventive Services Task Force Grades of Evidence scheme (see Table 1)[4]

Overall, these 3 observational studies, which bear an evidence grade of II-2 (Table 7), suggest that RTs have greater expertise regarding inhaler devices than other health care providers and, by virtue of this greater expertise, seem to "add value" to ambulatory care in that task.

RTs have also been compared to other health care providers regarding their attitudes about health promotion and counseling.[34] Specifically, Sockrider et al[34] compared survey results from 397 RTs (41% of whom were students in 3 regions) to those from 5,744 medical students in 13 schools. Though the RTs' survey responses were collected more recently (1993–1996) than those of the medical students (1991), the results suggested that RTs were more attentive and committed to disease prevention and promotion. In particular, there was general agreement among RTs about using part of each health encounter to promote prevention, that prevention counseling was as important as giving medication, and that learning counseling techniques was as important as learning about therapy. RTs generally disagreed that only physicians could teach patients how to take and adjust asthma medications. Finally, compared to medical students, RTs generally reported more favorable attitudes regarding prevention ($p < 0.004$). Specifically, RTs were significantly more likely ($p < 0.0001$) to take time to counsel on health promotion and to advise older patients to stop smoking, and placed greater value on smoking counseling than on other aspects of care. Overall, the authors concluded that, although some specific aspects of RTs' preventive practices warranted improvement (eg, the need to encourage influenza vaccination), RTs generally showed positive attitudes toward health counseling and prevention. This greater enthusiasm for health promotion and counseling, at least compared with medical students, encourages RTs' expanded role in ambulatory care. At the same time, the results of this survey invite further study to assess the clinical impact of these health prevention attitudes. Because these findings are based on only a single observational study, the evidence regarding RTs' relative effectiveness as health counselors bears an evidence grade of III (see Table 7).

Other ambulatory care roles in which RTs have been studied include smoking cessation counseling[35] and educating medical students in arterial blood sampling (see Table 7).[36] Specifically, Cohn et al reported that a 6-week smoking cessation program run by pediatric RTs achieved an end-program abstinence rate of 44% among 111 participating parents.[35]

Finally, RTs have been evaluated as educators of other health care providers. Specifically, Fagan and Cece[36] reported an experience in which RTs organized a program for teaching third-year medical students how to draw arterial blood. Using a 3-part program of didactic lectures, a quiz, and supervised draw of at least 2 ABG samples, 97% of the 31 participating medical students satisfied competence criteria.

Overall, regarding RTs in ambulatory care, the sparse available evidence invites much greater attention to RTs' effectiveness in this clinical venue. The studies regarding smoking cessation counseling and ABG training bear an evidence grade of III.

Conclusions and Future Investigative Needs

Based on this review of the available evidence regarding RTs' effectiveness, I believe the following conclusions can be offered. First, there is a substantial and growing body of evidence that supports RTs' effectiveness in a variety of care settings. The evidence is strongest for roles that have been addressed by randomized controlled trials comparing RTs' effectiveness with that of other health care providers, including physicians (see Table 4). These roles include weaning patients from mechanical ventilation under the guidance of respiratory care protocols and conducting protocol services to allocate non-ICU adult inpatient respiratory care. Though supported by lower grades of evidence than randomized trials (eg, observational cohort studies and descriptive studies), RTs' effectiveness in other roles is also suggested.

Notwithstanding the considerable body of evidence that buttresses RTs' role in health care, it seems more important in this forum to recognize gaps in current understanding and the need for further study to better clarify ways of optimizing the delivery of respiratory care. Indeed, the fact that respiratory care departments continue to be "decentralized" and that RTs' roles in some settings (eg, skilled nursing facilities) continue to be constrained and threatened under the crush of declining reimbursement indicates some ongoing uncertainty and controversy about whether RTs are cost-effective and/or better than other possible providers of respiratory care services. Because controversy can only exist in a vacuum of data, this remaining uncertainty underscores the need for more rigorously designed studies that compare various providers to assess who provides the best, most effective care.

In this context, what additional studies are needed? In the ICU, though concordant results support RTs' role in weaning, RTs' many other roles in ICU care warrant further study. For example, although RTs' superior knowledge of ventilators and of the modes of ventilation is widely appreciated by ICU physicians, studies comparing RTs' knowledge with that of other providers (as has been done regarding pulse oximetry,[37] metered-dose inhalers,[31–33] and prescribing inpatient respiratory care[30,31]) are needed. RTs' knowledge of cardiopulmonary physiology invites their expanded roles in other ICU functions, such as obtaining and interpreting hemodynamic studies, supporting extracorporeal membrane oxygenators, and administering nitric oxide. Indeed, RTs currently perform these roles in some settings, but evidence of their effectiveness is lacking and is needed. Finally, RTs' technical prowess invites more widespread adoption of their roles in performing ICU procedures, including placing indwelling arterial lines, intubation, and assisting at bronchoscopy. In addition, expanded procedural roles are possible with adequate training and monitoring (eg, placing central lines and performing routine bronchoscopic suctioning), though expansion to these roles will require robust training and ample supportive research.

Beyond the ICU, the research needs are equally compelling. Although available randomized trials establish RTs as effective allocators of adult non-ICU inpatient care in academic centers where protocol services have been carefully implemented and monitored,[30,31] widespread adoption of this role in other settings will require more study. Specifically, the generalizability of these conclusions to other settings and patient groups, such as community-based hospitals, extended care facilities, and pediatric patients requires urgent and rigorous attention.

Finally, of the 3 venues considered in this analysis, RTs' effectiveness in ambulatory care roles seems least well-studied or established. As with studies of nurse practitioners managing patients with common ambulatory problems,[38] so too should be studied RTs' roles in improving the care of patients with asthma, chronic obstructive pulmonary disease, pneumonia, and other common ambulatory respiratory problems. As an example, in the appropriate context, one could imagine a randomized controlled trial comparing the management of patients with mild to moderate asthma by RTs guided by algorithms versus the usual physician-directed care.

While we are thinking expansively about new and evolving roles for RTs, it is essential to establish criteria that must be satisfied in order to fully endorse these expanded roles. First, as has traditionally been practiced, I believe that close collaboration with physicians (eg, medical directors) who have appropriate expertise in pulmonary/critical care medicine and/or anesthesiology is needed. This model of teamwork interaction has many advantages, including allowing multidisciplinary input into care, collective commitment to the implementation and maintenance of high-quality protocols, and ongoing advocacy of RTs' roles.

Second, in order to gain acceptance in these expanded roles, RTs must demonstrate competence similar to or better than other providers at similar or lower cost. This requirement has already been satisfied by the results of the 5 available randomized trials (see Table 4),[13–15,30,31] but further evidence in other roles is needed.

Third, while studies of new roles for RTs are likely to emanate from respiratory care departments in academic medical centers committed to implementing and evaluating high-quality protocol programs, widespread endorsement will require evidence that RTs can confer similar benefits in other settings, including community-based hospitals, nursing homes, and extended care facilities. Greater attention to research in these settings is also clearly needed.

So, are RTs effective? The evidence assembled since Dr Egan's early vision suggests the answer: Yes, you are effective and you add great value to current health care. At the same time, the current health care climate offers opportunities and demands that you both practice and evaluate effective health care in new roles throughout an expanding spectrum of health care delivery. Because one dimension of being an effective health care provider is having the talent and rigor to study effectiveness and to use research findings to optimize effectiveness, respiratory care must continue to cultivate its ability to provide optimal care and to study it. My hope is that Dr Egan would be as pleased to see his vision becoming realized as I have been to present the 27th lecture that bears his name.

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Handbook of Hemodynamic Monitoring. Gloria Oblouk Darovic RN CCRN and Cory M Franklin MD. Philadelphia: WB Saunders. 1999. Soft-cover, illustrated, 392 pages, $24.95.

One of the most important 20th-century innovations that will continue to affect the delivery of health care in the 21st century is the advent of electronic monitoring devices. Microprocessors have provided the potential for incredible accuracy of hemodynamic measurements among critically ill patients in intensive care units. With this potential for information gathering, however, the need arises for skilled physicians, nurses, and respiratory therapists who understand the capabilities and limitations of these monitoring devices and who are capable of interpreting measurements and utilizing the information to make clinical decisions. The authors of **Handbook of Hemodynamic Monitoring** have accurately stated that monitoring of the critically ill patient involves a number of factors, including those related to the patient's disease state, the monitoring equipment in use, and the effect of obtaining hemodynamic data on a given patient. This handbook is a storehouse of information designed to enable clinicians to obtain a working knowledge of hemodynamic monitoring devices and the information they provide.

Overall, the book achieves its goal of emphasizing relevant points of clinical monitoring techniques, providing diagnostic and therapeutic principles related to cardiopulmonary disease, and providing clear summaries of important concepts presented in the text. One of the strengths of this book is its organization, which moves logically from basic concepts (such as anatomy and physiology review) through assessment and basic monitoring skills, to applications regarding specific disease states. Summary tables provide lists of pertinent facts for quick reference. Drawings of devices, such as catheters and transducers, help to demystify some of the sophisticated equipment used in the intensive care unit. Illustrations of important physiology concepts, such as depiction of the normally low intracellular oxygen requirement, which emphasizes the inherent oxygenation safety margin that exists in the tissues, serve to move the critical care clinician to a deeper level of understanding of the capabilities and limitations of the cardiopulmonary system.

While a good background in cardiopulmonary anatomy and physiology is assumed, brief reminders of salient points are included in the text to jog the memory and obviate looking up information that may no longer be fresh in the reader's mind. The authors are to be commended for use of up-to-date breath sounds terminology while also including parenthetical references to older terms that may still be in clinical use.

Another unique aspect of this handbook is the inclusion of nursing "gems" that will benefit respiratory therapists and medical and surgical residents alike. Descriptions of physiologic phenomena, such as S_3 and S_4 cardiac sounds and gallop rhythms, are very useful in aiding the novice in discerning subtle differences among heart sounds.

Descriptions of hemodynamic monitoring device setup and calibration techniques will be invaluable to nurses as well as to respiratory therapists. While physicians may not typically assume responsibility for setting up and maintaining hemodynamic monitoring equipment, knowledge of calibration and zeroing techniques will aid them in determining if a questionable measurement on a given patient is reliable. The authors have done an excellent job of detailing setup and sampling from fluid-filled systems, as well as describing appropriate techniques for insertion of arterial and central venous lines. While the text is not intended to be a substitute for individual training in these techniques, it serves as a useful reminder of steps for the trained clinician.

Troubleshooting tips for hemodynamic monitoring systems in general are very good throughout the book. The text also includes a section on catheter-related problems such as sepsis, general pharmacologic management of hemodynamic conditions, and special devices such as intra-aortic balloon counterpulsation. The section on intra-aortic balloon counterpulsation is especially good in that it clearly describes normal and abnormal wave forms and gives excellent troubleshooting information about a device that may not be used on a regular basis by all clinicians.

The authors have provided valuable information about treatment of specific disease states. In the section covering various types of shock they provide a simple but comprehensive outline of treatments based on cause. There are also excellent reviews of multiple organ dysfunction syndrome, acute respiratory failure, and acute respiratory distress syndrome, emphasizing similarities among these diseases, as well as their differences. The sections covering heart disease, whether ischemic, related to valvular abnormalities, or of structural or systemic origin, are comprehensive and include not only information about the disease process itself, but also about management in the context of hemodynamic implications.

Although the text is clearly written, logically sequenced, and includes a good list of suggested reading material, there are a number of typographical errors, and I found a couple of instances of incorrect content. On Page 8, Section A ("Decreased Lung Compliance"), the bullet point states that ". . . a gradual increase in peak inspiratory pressures (PIP) to > 30 cm H_2O indicates a gradual *increase* in lung compliance. . . . " The text should read ". . . a gradual increase in peak inspiratory pressures (PIP) to > 30 cm H_2O indicates a gradual *decrease* in lung compliance. . . . " On Page 64, in Section 2, the text refers to the ease of visualization of the *external* jugular veins, but the text is meant to reference the *internal* jugulars, which are used to assess jugular venous distention because of their size and location. Also, a potential source of confusion involves the electrocardiogram (ECG) tracing shown on page 63. The tracing represents a "*bigeminal ECG with pulse deficit*" in which the second beat is a nonperfusing beat. While technically correct (ie, a bigeminal ECG rhythm displays paired beats), the more commonly used clinical definition of ventricular bigeminy involves alternation of premature ventricular contractions with supraventricular beats. The tracing shown in the book more closely resembles couplets (2 premature ventricular contractions in a row), but without the presence of normal QRS waves. Future editions of the book may be improved by use of a different tracing to illustrate the phenomenon of non-perfusing beats.

Despite the errors just mentioned, the **Handbook of Hemodynamic Monitoring** should be a valuable addition to the pockets of clinicians who work closely with hemodynamically-compromised patients. The spiral-bound format is excellent for accessibility, and the consistent layout of each chapter contributes to the usefulness of this book as an important tool for management of patients requiring hemodynamic monitoring. There are no internal citations in the text, but the list of suggested readings at the back of the book appears to be the source from which material for the book was compiled. As such, these sources are current and appropriate.

In summary, the authors have put together an attractive, clinician-friendly, comprehensive handbook on hemodynamic monitoring of the critically ill patient. Its pocket size makes it a readily available reference book that may be carried with the practitioner in the intensive care setting. Nurses, respiratory therapists, and residents may benefit most from this book, as will students of each of those disciplines. Its primary limitation is the number of typographical and other errors, as mentioned, but the bulk of the text is concise and correct.

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Kendig's Disorders of the Respiratory Tract in Children, 6th edition. Victor Chernick MD and Thomas F Boat MD, editors, and Edwin L Kendig Jr MD, consulting editor. Philadelphia: WB Saunders. 1998. Hardcover, illustrated, 1,213 pages, $215.

Kendig's sixth edition of **Disorders of the Respiratory Tract in Children** is a comprehensive textbook covering all aspects of lung disease in children. The new edition has several new chapters, with increased clinical discussions of diseases such as human immunodeficiency virus and improved discussions of lung development and physiology. The editors have directed this "encyclopedic" text toward the pediatric clinician, but the contents are applicable to any health professional who cares for children with lung disease. Importantly, this text is organized primarily by disease and not by symptom. Therefore, while an exhaustive discussion of a known disease is provided, the text is not written to easily provide help with differential diagnosis in a patient with a specific symptom.

The book's organization is mostly the same as previous editions. Occasionally this can be confusing, for example, viral pneumonia is under "infections" while pertussis is under "other diseases". The new chapters on molecular determinants of lung development and developmental physiology are outstanding for understanding normal and abnormal determinants of lung development. Likewise, a new chapter on bronchoscopy corrects a major deficiency in previous editions. In the section devoted to infections, the new chapter on infections in immunocompromised hosts provides a clear guide to clinical evaluation and diagnosis. This chapter is complemented by a chapter on pulmonary disorders in pediatric HIV infection. The editors have been able to keep the writing style easy to read and comprehend. There are exhaustive lists of references at the end of each chapter, most with current updates to previous editions.

As with any text, newer therapies may be missing or only covered briefly. Nitric oxide therapy for persistent pulmonary hypertension of the newborn is only briefly mentioned, with no specific management guidelines. There is little mention of noninvasive ventilation, an increasingly common therapy for children. Also, the chapter on sleep disorders is limited to obstructive sleep apnea and congenital hypoventilation syndrome, with almost no discussion of noninvasive ventilation for either of those diagnoses.

One area of concern is the recommended clinical management of asthma. While the author provides an excellent review of pathophysiology and diagnosis, her treatment recommendations differ in several areas from those of the National Institutes of Health and international guidelines. These differences will probably not affect clinical outcome, but they can cause confusion with efforts to standardize care.

This book is pleasing to read, with chapters organized similarly throughout. The figures, radiographs, and pathology plates are clear, and well marked with informative legends. The index is exhaustive and easy to navigate. Overall this is an excellent textbook on respiratory diseases of children. It is designed as a comprehensive reference text and not a clinical guide or "how-to" therapy text. Each chapter includes an exhaustive discussion on the pathophysiology, diagnosis, and treatment of a specific disease or infection. This improved new edition continues to be an outstanding reference for medical professionals who treat children with respiratory disorders.

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Lecture Notes on Respiratory Medicine, 5th edition. SJ Bourke MD and RAL Brewis MD. Oxford, United Kingdom: Blackwell Science. 1998. Soft-cover, illustrated, 205 pages, $34.95.

This book provides a clearly written overview of the field of respiratory medicine and is written with medical students and general practitioners in primary care as the target audience. The book is a good introduction to the field of pulmonary medicine for medical students and residents, and is a useful resource for the busy generalist physician. Respiratory therapists and nurses involved in the care of pulmonary patients outside the intensive care unit will also find this book clinically relevant and highly readable.

The initial part of the book provides an introduction to respiratory medicine: these chapters introduce the reader to basic anatomy and physiology, pulmonary function testing (PFT), chest radiology, and pertinent aspects of the clinical history and examination. The authors do not assume the reader is already familiar with this subject matter, and they have written an excellent introduction to these subjects in a concise, coherent text. The chapter on PFT, in particular, is clearly written, with good use of illustrative diagrams to complement the text. There are numerous examples of abnormal spirograms and flow-volume loops, which will be particularly helpful to students and practitioners new to this technology. This chapter is a good introduction to the principles underlying PFT, and the use of clinical cases helps to illustrate the practical relevance of those principles. Also included in this part of the book is a chapter on radiology, which has an introduction and guide to the interpretation of chest radiographs and is supplemented with examples of abnormal radiographs. The chapter also introduces the reader to the anatomy of images viewed by chest computed tomography. However, with the importance of chest computed tomography to the practice of pulmonary medicine, the chapter would probably benefit from the inclusion of representative computed tomography images.

The second and major part of the book describes the major diseases of the respiratory system. These chapters are organized by disease category; each chapter includes details on epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment. These chapters are easy to follow, with major points in the text supplemented by numerous diagrams and tables, and provide an overview of many complex diseases in a remarkably concise text. A major strength of this section is the inclusion of representative chest radiographs accompanied by case histories. These clinical vignettes help reinforce important details in the text and illustrate the clinical and practical importance of this text to the reader.

The authors had to be highly selective, given the space limitations of this format ("Lecture Notes"). They have chosen to give more space and detail to commonly encountered pulmonary problems than to the rare conditions that pulmonary physicians are fond of discussing in detail. The text includes good information on evaluating and treating these common clinical scenarios, and this is a highly appropriate focus for a book aimed at students and primary care physicians. However, for an American reader, there are a few obvious idiosyncrasies in this book written in the United Kingdom. For example, the recommendation to use amoxycillin alone as the first-line agent in the treatment of outpatient community-acquired pneumonia reflects the British Thoracic Society's guidelines to cover *Streptococcus pneumoniae* as the preeminent pathogen in such patients. In the United States it is customary to include coverage for "atypicals" such as *Mycoplasma pneumoniae* by using, for example, a macrolide.

Also of interest to many readers will be the screening recommendations for tuberculosis. These recommendations reflect current practice in the United Kingdom, where bacillus Calmette-Guerin vaccination is customary. Consequently, skin testing for immune responses to tuberculosis obviously has a different implication in the United Kingdom than in the United States. In the United Kingdom the bacillus Calmette-Guérin-immunized population is expected to have a positive skin test, whereas in the United States a positive skin test is taken to indicate latent tuberculosis infection.

The introductory chapter on PFT also includes an example of differing clinical practice in the United States and United Kingdom: the authors note that restrictive disease may be diagnosed when both forced expiratory volume in the first second and forced vital capacity are similarly reduced. In the United States it is customary to proceed to the measurement of lung volumes to avoid the spurious diagnosis of restriction in patients with such abnormal spirometry due to severe obstruction. Apart from these isolated examples of disparate clinical practice, the book is highly relevant to any practitioner in the United States. The book is obviously written for practicing clinicians and typically offers a sensible, straightforward approach to problems encountered in everyday clinical practice.

While the length and nature of the text limit the amount of detail that can be included, for the interested reader each chapter is followed by a bibliography of 5 to 6 references. Though short, the lists typically include both seminal articles and references to more in-depth review articles that will be a useful starting point for those seeking more detailed information on a topic. The text is supplemented with numerous diagrams, tables, and graphics that complement the body of the text. Important clinical problems are also illustrated by radiographs and case histories; these contribute to the relevance of the book by emphasizing important problems likely to be encountered in everyday clinical practice. This book is well organized and clearly presented, with good attention to detail, making this concise book an excellent overview of the field of respiratory medicine.

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Cardiopulmonary System Daniel R Richardson PhD, David C Randall PhD, Dexter F Speck PhD. Integrated Medical Sciences Series. Madison, Connecticut. Fence Creek Publishing. 1998. Soft-cover, illustrated, 353 pages, $24.95.

Over the past decade, medical schools have increasingly begun to revamp their curricula in response to criticism that they had not kept pace with medical advancement and that their curricula consequently held little or no clinical relevance. Predictably, conveying the clinical relevance of the conceptual aspects of physiology to medical students and medical practitioners has been a persistent and growing challenge. Additionally, physiology is frequently presented fragmented, organized by individual structures or components independently of each other. With this book the authors attempt to emphasize the interdependence of organ systems—specifically within the cardiopulmonary system—utilizing the concept of homeostasis while maintaining clinical relevance by framing chapters with clinical scenarios, followed by explanations couched in physiological concepts. To these ends, the authors are variably successful.

Broadly, the text is composed of 4 main sections, though of unequal lengths and emphasis. The first section, Chapters 1 through 6, covers the basic concepts of physiology pertaining to future discussions and begins with an explanation of homeostasis, the central concept around which the text is organized. It continues with brief discussions of relevant concepts of physics, physiology of muscle function, basic anatomy, and blood composition and behavior.

The second section mirrors the first by beginning with a chapter devoted to homeostasis, but in the context of the cardiopulmonary system and those components that function to maintain homeostasis of blood pressure. Chapter 8 covers cardiac electrophysiology and is by far the longest and most complicated. It introduces the reader to the Nernst equation, explaining in detail the ionic basis of the ventricular muscle action potential, and comparing this to the sino-atrial nodal action potential. The chapter continues with an explanation of the electrocardiogram and concludes with a brief introduction to clinical interpretation of abnormal cardiac tracings. The next 2 chapters are devoted to a description of the normal cardiac cycle, utilizing the obligatory pressure-volume curves, a discussion of Starling's Law, and the effects of preload and afterload on cardiac function.

Chapters 11 and 12 describe the regulation of tissue blood flow and the mechanisms of blood-tissue exchange of metabolites and oxygen/carbon dioxide. The final chapter in this section discusses the control of the cardiovascular system in maintaining blood pressure and normal venous blood return. It reviews the neurogenic control of systemic blood pressure via sympathetic and parasympathetic pathways originating in the aortic arch and carotid sinus bodies.

The third section of the book is devoted to the respiratory system and begins with Chapter 14. The chapter reviews the measured lung volumes and capacities, using a standard spirometry tracing. Chapter 15 introduces the concepts of airway resistance and lung/chest wall compliance. The ubiquitous flow-volume curves are also introduced and explained in this chapter. Chapter 16 discusses pulmonary vascular dynamics and both active influences (eg, hypoxic vasoconstriction) and passive influences (eg, gravity) on resistance. There is a brief description of West's 3 zones of the lung and of the ventilation-perfusion ratio. The last 2 chapters in this section discuss blood-gas exchange and the role of the cardiopulmonary system in maintaining acid-base homeostasis. This is where the hemoglobin-oxygen dissociation curves are explained, as well as the importance of the Bohr and Haldane effects. The last chapter in this section describes the components that control the respiratory drive.

The final section of the book is composed of one chapter and is intended to reinforce the interdependence of the 3 major components of the cardiopulmonary system: the heart, lungs, and circulation. The authors use descriptions of the response of the cardiopulmonary system to exercise to illustrate this interdependence.

On the whole, the book seems to accomplish the authors' goal of presenting key concepts of cardiopulmonary physiology successfully in a "systems" approach while integrating patient-oriented cases, thereby reinforcing the clinical relevance of the subject matter. The text is very clearly written and logically presented. The illustrations and highlighted key points were concise and a tremendous asset. The theme of homeostasis was well chosen and appropriately emphasized throughout the book and the use of summary sections and review questions helped to reinforce the subject matter. The appendix of abbreviations is helpful for those using the book as a reference, and the index is well organized. Finally, the book is attractive in layout and in design, the font is clear and easy to read, and there are few, if any, typographical errors.

There were few detractions from the book, and they centered primarily on the length and detail of the cardiac system description. I found that the description of the cardiac electrophysiology system in Chapter 8 was written in much more detail than the rest of the textbook. In addition to this inconsistency, Table 8–2, describing normal and pathophysiologic changes of electrocardiogram components, was poorly laid out and contained too much clinical material. Indeed, although the clinical scenarios served to strengthen most points and to introduce forthcoming chapters, several distracted the reader with irrelevant information.

The book is one of ten in a series intended for medical students as course supplements and aids for board review. Certain aspects of the book, however, would also be helpful for other health care specialists. Clearly the book is an easier read than Guyton's *Textbook of Medical Physiology*, although much less detailed. Most helpful would be the sections describing the cardiac cycle and pump function, mechanics of the respiratory cycle, including flow-volume curves, and the section on basic acid-base disturbances. However, I would recommend use of a more comprehensive text on electrocardiogram interpretation before referring to this text's section on cardiac electrophysiology.

In summary, **Cardiopulmonary System** is a well-written text with clear illustrations that reviews key concepts of physiology in a clinical context. It is primarily intended as a course supplement for medical students but may be of use as a quick reference for those health care professionals who require an intimate knowledge of the cardiopulmonary system.

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Lung Function Tests: Physiological Principles and Clinical Applications. JMB Hughes and NB Pride, editors. Philadelphia: WB Saunders. 1999. Softcover, illustrated, 314 pages, $39.95.

I picked up this book with great expectations. First, both editors are well known to me because of their considerable contributions to the field of pulmonary physiology. The second reason I was interested in this book was that, according to the preface, the bases for the chapters of the book were lectures given by the authors at a course given at the Hammersmith Hospital between 1980 and 1995. Being frequently called upon myself to give such lectures, why not see how others did it? Do they stress the same things or cover different topics? After all, it's not unlike fishermen comparing secrets and techniques as to how they caught the "big one." Lastly, since the authors are British I could safely assume that the book was likely to be well written. I am happy to report that all these expectations turned out to be true.

The preface tells us that the topic material for each chapter was originally designed for physicians. However, as attendance at the course changed over the years, the material was also changed to appeal to the persons charged with the responsibility for performing the tests, who, in the United States, are respiratory therapists. The authors specifically point out that, "laboratory staff need a good knowledge of the underlying physiology and clinical indications for these tests." However, the book is not meant to be a technical manual; rather it is to be used to answer the questions as to why a particular test is ordered and what the results mean.

The book is divided into 19 chapters, each author being an acknowledged expert in the field. In addition, there is a glossary of abbreviations (much needed in pulmonary physiology) and an index at the back of the book. The chapters of the book are further organized into 4 sections. Section I deals with spirometry, air flow resistance, lung volume and elasticity, and the respiratory muscles. Section II deals with gas exchange, diffusing capacity, control of breathing, dyspnea, and exercise testing. Section III deals with some very unusual topics for books of this genre. These topics include sleep-disordered breathing, pediatric pulmonary function, pulmonary function tests (PFTs) in the intensive care unit, and home oxygen, as well as house-based mechanical ventilation. The last section (Section IV) deals with some miscellaneous topics, including cough and bronchial challenge, surgical assessment, pulmonary vascular disease, case studies, and presentation of results.

As it stands, these topics are very complete and yet extend the usual scope of topics found in such books. I know of no other book on lung function that so completely covers such a broad range of topics on PFTs.

Let's look at a few chapters to get a feel for this book. Chapter 1 deals with the old standard of spirometry. There are excellent illustrations throughout the chapter. Right off the bat the author gets into the important but often not covered topic of the difference between (and usefulness of) slow and fast vital capacity. Some unusual topics include maximum expiratory flow-volume maneuvers performed through the nose, an excellent explanation of upstream resistance–lung recoil curves, explanations of negative expiratory pressure, and tidal volume maneuvers. One minor complaint is that the references at the end of this and other chapters are limited.

The next chapter, on airway resistance, is similar in approach and scope. There is a short but excellent review of lung mechanics, followed by an excellent review of all the various techniques by which airways resistance can be assessed, including esophageal balloon techniques, forced oscillation, and flow-interruption approaches.

The next chapters are uniformly excellent but suffer, as all such books suffer, from some inconsistencies from chapter to chapter, because each is written by a different author. All chapters include material not commonly found in other books. The figures (often the most useful part of a book) are uniformly better than average. The style, while somewhat inconsistent, is generally clear and concise. As the authors are British, the use of language is precise, but throughout the book terms are used that are not in common use in the United States; the glossary at the end, however, will be very helpful to the reader when coming across an unknown term.

Another chapter to note is the one written by Michael Silverman and Janet Stocks on pediatric lung function. During the period of time that I was reviewing this book, I had to prepare a lecture on pediatric lung function testing for a national meeting. Reading a chapter on this particular topic was very timely, because I drew extensively from it in preparation for my lecture. The illustrations, in particular, were very helpful. This, as well as other chapters (for example, Chapter 8, "Measurement of Breathlessness") have detailed pros and cons of each technique presented; this is also very useful. The highlighted summary at the end of each chapter, as well as the attendant references, were most welcome and will be helpful to anyone new to the field. Moreover, these touches bring a needed degree of consistency to each chapter.

Another chapter of particular interest is Chapter 14, which covers bronchoprovocation and assessment of cough. The material presented is very complete and also covers the issues of tests that do and do not require a deep inflation—again a topic not often covered. The author introduces the controversial notion that bronchoprovocation agents can affect airways narrowing by both direct and indirect (secondary) mechanisms—a notion not embraced by all. There is a nice section on safety and patient preparation. However, one is disappointed by the author's failure to provide examples of tests, and the section on interpretation lacks specifics *needed* for interpretation; for example, the dose of methacholine usually considered normal ($>$ 8 mg/mL) was not discussed. The authors do cover bronchodilator studies but again fail to provide criteria for a positive study.

I found some parts of the book to be less helpful. First, it is unclear why a second chapter (Chapter 17) was included on the diffusion capacity of the lung for carbon monoxide (D_{LCO}). This PFT is, by most accounts, one of the least useful and most variable of the tests that are performed by the PFT lab. The contents of the chapter suggest that this is a personal expertise of the author, but even so it is unclear why other more useful topics such as spirometry did not receive similar treatment. The last two chapters (18 and 19) are not very useful. Chapter 18 contains case examples. Now, I am the first one to advocate the use of case examples to teach about the utility of PFTs; unfortunately, these cases are very cryptic, and as they are missing diagrams of results (eg, flow-volume loops), they are not very helpful. This is particularly odd given that Chapter 19 deals with data presentation. In the latter chapter, much of the material on data presentation is confusing and incomplete. The treatment of reference values is also very cursory. This topic, in my experience, is a difficult one for many, and a better treatment of this important topic would be expected from these authors. However, these criticisms, with the exception of the point about the reference equations, are all minor deficiencies.

The book is a paperback with a somewhat busy cover of diagrams taken from the text. I noted no typographical errors in the material that I read carefully. The references, though few, are timely and include most of the important references for the topic of lung function.

In summary, this book is well written and organized, providing the reader with an up-to-date, comprehensive treatment of pulmonary function testing. Its utility is the inclusion of topics not normally covered by other texts and also its excellent illustrations. There are a few shortcomings noted, but these are not enough to deter me. Accordingly, I strongly recommend this book to anyone interested in advanced education in pulmonary physiology, and to anyone interested in PFT, as one of the few books that does a truly excellent job with both topics.

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All You Really Need to Know to Interpret Arterial Blood Gases. 2nd edition. Lawrence Martin MD. Philadelphia: Lippincott Williams & Wilkins. 1999. Softcover, illustrated, 254 pages, $31.95.

A newly released second edition, this softcover book has been enhanced with additional information for the medical practitioner. This 1999 version goes beyond just interpretation of arterial blood gases. Dr Martin has included additional sections on:

- Mixed venous sample interpretation
- Review of noninvasive measures: pulse oximetry and end-tidal CO_2
- Correlation of arterial samples with noninvasive assessments
- Electrolyte interpretation
- Anion gap in-depth explanation
- Putting it all together: clinical evaluation and test ordering

The book includes a handy "Quik-Card" for blood gas interpretation and a short 'before and after' test for readers to evaluate their skills. Before Chapter 1 starts, the book opens with a new section called "Quik-Course on Blood Gas Interpretation." These

13 pages give a synopsis of each chapter in the book. It is suggested that the Quik-Course can be used as a starting point to study, as a final review, or as a refresher down the road. The book has 13 detailed chapters with *really* everything you need to know to interpret blood gases, arterial or venous, co-oximetry, electrolytes, and acid-base disorders. In the back are appendixes containing symbols, abbreviations, a glossary of terms, and both classic and up-to-date references. Chapters on case studies, free text interpretations, and clinical evaluation and test ordering pull all the information together to make this book a great educational tool.

This book is intended for respiratory therapy students, therapists, technicians, medical students, interns, residents, nurses, physicians, and all other health care professionals who "want to learn the art and science of blood gas interpretation." Any health care provider involved in critical care or pulmonary diagnostics would want to have this book in his or her personal library. In his preface, Dr Martin states that, "If you read carefully through each chapter and work on all the problems and exercise, you should acquire sufficient expertise to *teach* the subject." This affordable book should be mandatory reading for anyone who needs to understand and interpret these important blood samples and their relationship to a patient's clinical pulmonary and acid-base status.

Dr Martin included the original preface from the first edition along with a new one for this second edition. In the 2 prefaces he covers a little history of blood gases, along with stating the book's intentions and emphasis. He achieved his goals and really "put it all together" for the reader. The book is well organized in the flow of material presented: concise yet complete. Dr Martin has included graphs, illustrations, and pictures to demonstrate the material covered in each chapter. The graphics and illustrations expand the information covered in text discussions to assist all styles of learners to understand the physiology covered in the book. The reader will want to have paper and pencil handy when reading this book, as it will truly enhance learning through practice. Chapters 1 through 8 have clinical problems strategically placed throughout the text. These problems are easily identified in boxed shaded areas, with answers in the back of each chapter, along with the reasons why other responses are incorrect. As Dr Martin suggests, optimal learning occurs when the reader calculates the problems in written form, not mentally, before checking answers.

The information presented in each chapter is quickly put to practical use, reinforcing learning without having to memorize material. There are additional questions marked by bold "?" symbols scattered throughout the chapters, with the answers immediately following, thus making the reader feel like they are having a conversation with the author. I found this an easy book to read and understand. The chapters are well written and researched. The material in the chapters does not have numbered references; rather, at the end of the book, references are mentioned that were used for each chapter. Illustrations borrowed from other publications are footnoted with the reference directly beneath it.

Chapter 1, "What is Meant by Interpreting Arterial Blood Gases," covers the basic information needed to evaluate the results of a blood gas analysis. Chapter 2, "Three Physiologic Processes, Four Equations," reviews the P_{CO_2} (partial pressure of carbon dioxide) equation, the alveolar gas equation, the oxygen content equation, and the Henderson-Hasselbalch equations in depth. Chapter 3 covers the relationship between P_{aCO_2} (arterial partial pressure of carbon dioxide) and alveolar ventilation. A new section is added to this chapter on capnography, the noninvasive measurement of end-tidal P_{CO_2}. Chapter 4 discusses P_{aO_2} (arterial partial pressure of oxygen), alveolar-arterial P_{O_2} difference, and P_{aO_2}/F_{IO_2} (ratio of partial pressure of oxygen to fraction of inspired oxygen), including the importance of barometric pressure on oxygenation calculations. Chapter 5 covers the relationships between P_{aO_2}, S_{aO_2} (arterial oxygen saturation measured via arterial blood sample), and oxygen content in evaluating how much oxygen is in the blood. Dr Martin expanded Chapter 6 on the clinical use of and differences between S_{pO_2} (oxygen saturation measured via pulse oximetry) and S_{aO_2}. The chapter illustrates the potentially critical difference between S_{pO_2} and S_{aO_2} when carboxyhemoglobin and methemoglobin are involved in a case. This is an important area of pulmonary and critical care information that is frequently lacking in the education and training of nonpulmonary, nonrespiratory health care providers. I found the material in Chapter 6 excellent—the most complete I have ever read. The addition of noninvasive measures (pulse oximetry and end-tidal carbon dioxide) and their correlation to blood gas, co-oximetry, and electrolyte results bring the material in this second edition up to date with technological advances.

Chapter 7 addresses the relationships between pH, P_{aCO_2}, electrolytes, and acid-base status. Chapter 8 delves into the complexities of primary and mixed acid-base disorders. The 5 case studies in Chapter 9 help the reader "put it all together." All the information learned in the text is put to use, as each case has numerous questions and problems to answer. As with previous chapters, the answers and explanations are in the back. Chapter 10 has 20 case studies where no questions are asked. In these scenarios, a brief history is given, along with blood gas, co-oximetry, and/or electrolyte results. For each case, the reader is asked to evaluate the patient's status for oxygenation, ventilation, and acid-base. Again free text interpretations by the author are provided at the end of the chapter. Chapter 11, new since the first edition, covers clinical evaluation and test ordering through 16 brief cases. This chapter would be most beneficial for medical students and residents or respiratory students studying for clinical simulations. Practicing respiratory care providers who work with protocols or need to advise medical staff would find this a helpful chapter. Chapter 12, also a new chapter for the second edition, covers mixed venous blood gas results. It is a well-written, helpful chapter but felt out of place at the end of the book after all the case studies. It would be appropriate to place this material between Chapters 6 and 7.

This softcover book is 6 inches by 9 inches and is one-half inch thick, with a colorful green jacket. The interior of the book is all black and white text, graphics, illustrations, and pictures. Colors would enhance the non-text material in this book but is not necessary to present the material and would surely raise the cost. All the graphs, charts, and illustrations are very clear and easy to understand.

I found a few typographical errors, one being recurrent. In several places, (pages xxiv, 15, and 37), P_{aCO_2} was written when the intent was to print P_{ACO_2} (alveolar partial pressure of carbon dioxide). The information was correctly provided on pages 17 and 50. The P_{ACO_2} typographical error would be initially confusing to the neophyte learner until they checked outside references or found the correct data on pages 17 and 50. The only other typographical error I found was on page 47, in the answer for clinical problem 3.10. The resting $\dot{V}_{CO_2}$ should be 200 mL/min, not 20 mL/min.

In the front of the book is a mention of the author's Web site, *http://www.mtsinai.org/pulmonary*. I happened upon that site before being asked to review the textbook, and I found it a great resource for new staff or students to review their skills in blood gas and pulmonary-related material. It is apparent from reading this book and reviewing the Web site that Dr Martin is an expert in the field, obviously extremely knowledgeable. He uses a style of writing that captures the interest of the reader, enhancing learning. The author definitely achieved his goals in providing material that allows a reader to interpret blood gases, electrolytes, co-oximetry, acid-base balance, and more. I would highly recommend this book as a valuable reference or training text, and as an addition to personal or departmental libraries.

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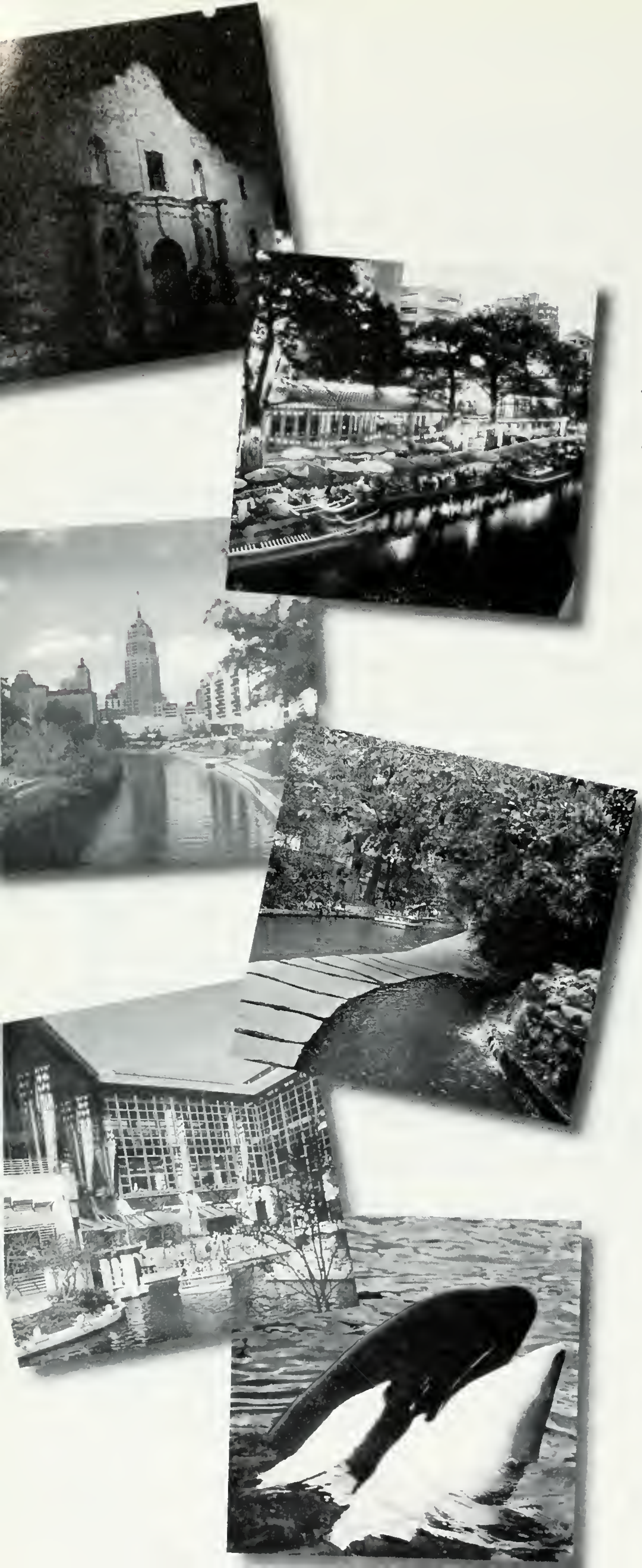

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call for abstracts

RESPIRATORY CARE • OPEN FORUM 2001

The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present posters at the OPEN FORUM during the AARC International Respiratory Congress in San Antonio, Texas, December 1-4, 2001. Accepted abstracts will be published in the October 2001 issue of RESPIRATORY CARE. Membership in the AARC is not required for participation. All accepted abstracts are automatically considered for ARCF research grants.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report **(1) an original study, (2) the evaluation of a method, device or protocol, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

ESSENTIAL CONTENT ELEMENTS

Original study. Abstract *must* include (1) Background: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

Method, device, or protocal valuation. Abstract *must* include (1) Background: identification of the method, device, or protocol and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

Case report. Abstract *must* report a case that is uncommon or of exceptional educational value and must include (1) Introduction: relevant basic information important to understanding the case. (2) Case Summary: patient data and response, details of interventions. (3) Discussion: content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

FORMAT AND TYPING INSTRUCTIONS

Accepted abstracts will be photographed and reduced by 40%; therefore, the size of the original text should be *at least* 10 points. A font like Helvetica or Times makes the clearest reproduction. The first line of the abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institution(s), and location; underline presenter's name. Type or electronically print the abstract *single spaced in one paragraph on a clean sheet of paper, using margins set so that the abstract will fit into a box no bigger than 18.8 cm (7.4") by 13.9 cm (5.5"), as shown on the reverse of this page.* Insert only one letter space between sentences. Text submission on diskette is allowed but must be accompanied by a hard copy. *Data may be submitted in table form, and simple figures may be included provided they fit within the space allotted. No figure, illustration, or table is to be attached to the abstract form.* Provide all author information requested. Standard abbreviations may be employed without explanation; new or infrequently used abbreviations should be spelled out on first use. Any recurring phrase or expression may be abbreviated, if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; and (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to Linda Barcus at (972) 406-4667.

Early Deadline Allowing Revision. Authors may choose to submit abstracts early. Abstracts postmarked by May 31, 2001 will be reviewed and the authors notified *by letter only* to be mailed by June 15, 2001. Rejected abstracts will be accompanied by a written critique that should, in many cases, enable authors to revise their abstracts and resubmit them by the Final Deadline (July 17, 2001).

Final Deadline. The mandatory Final Deadline is July 17, 2001 (postmark). Authors will be notified of acceptance or rejection *by letter only.* These letters will be mailed by September 1, 2001.

Mailing Instructions. Mail (Do not fax!) 2 clear copies of the completed abstract form, diskette (if possible), and a stamped, self-addressed postcard (for notice of receipt) to:

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RESPIRATORY CARE

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Categories of Articles

Research Article: A report of an original investigation (a study). Must include Title Page, Abstract, Key Words, Background, Methods, Results, Discussion, Conclusions, and References. May also include Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendices.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a topic that has been the subject of at least 40 published research articles. Must include: Title Page, Outline, Key Words, Introduction, Review of the Literature, Summary, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles. Same structure as Review Article.

Update: A report of subsequent developments in a topic that has been critically reviewed in RESPIRATORY CARE or elsewhere. Same structure as a Review Article.

Special Article: A pertinent paper not fitting one of the other categories. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper addressing an issue in the practice or administration of respiratory care. It may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A brief, signed communication responding to an item published in RESPIRATORY CARE or about other pertinent topics. Tables, Figures, and References may be included. The letter should be marked "For Publication."

Case Report: Report of an uncommon clinical case or a new or improved method of management or treatment. A case-managing physician must either be an author or furnish a letter approving the manuscript. Must include: Title Page, Abstract, Introduction, Case Summary, Discussion, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Must include: Title Page, Text, and References. May also include Tables and Figures (if so, must include Figure Legends).

Drug Capsule: A miniature review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, or pharmacotherapy.

Graphics Corner: A brief case report discussing and illustrating waveforms for monitoring or diagnosis. Should include Questions, Answers, and Discussion sections.

Kittredge's Corner: A brief description of the operation of respiratory care equipment. Should include information from manufacturers and editorial comments and suggestions.

PFT Corner: A brief, instructive case report including pulmonary function testing, accompanied by a review of the relevant physiology and appropriate references to the literature.

Test Your Radiologic Skill: A brief, instructive case report involving pulmonary medicine radiography and including one or more radiographs. May involve imaging techniques other than conventional chest radiography.

Review of a Book, Film, Tape, or Software: A balanced, critical review of a recent release. RESPIRATORY CARE does not accept unsolicited book reviews; please contact the Editor if you have a suggestion for a book review.

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Print on one side of white 8.5 × 11 inch paper, with margins of at least 1 inch on all sides. Double-space the text and number the pages. Do *not* include author names, author institutional affiliations, or allusions to institutional affiliations anywhere except on the title page. On the Abstract page include the title but do not include author names. Begin each of the following on a new page: Title Page, Abstract, Text, Acknowledgments, References, each Table, each Figure, and each Appendix. Use standard English in the first person and active voice. Type all headings in initial-capital letters (eg, Background, Methods, Patients, Equipment, Statistical Analysis, Results, Discussion). Center the main section headings and place second-level headings on the left margin.

Abstract. Please ensure that the abstract does not contain any facts or conclusions that do not also appear in the body text. Limit the abstract to no more than 400 words.

Key Words. Research, Review, Overview, and Special Articles require Key Words. On the Abstract or Outline page, include a list of 6 to 10 key words or two-word phrases.

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Article in a journal carrying pagination throughout the volume:

> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided, and those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in a journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

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> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990:76-85.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977:26-42.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

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Tables. Tables should be consecutively numbered. Start each table on a separate page. Number and title the table and give each column a brief heading. Place explanations in footnotes, including all nonstandard abbreviations and symbols. Key the footnotes with the following symbols, superscripted, in the table body, and in the following order: *, †, ‡, §, ‖, ¶, **, ††. Do not use horizontal or vertical rules or borders. Do not submit tables as photographs, reduced in size, or on oversize paper.

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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse
events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FDA Use Only (Resp Care)

Triage unit
sequence #

A. Patient information

1 Patient identifier

In confidence

2 Age at time of event: ____
or
Date of birth:

3 Sex
☐ female
☐ male

4 Weight
____ lbs
or
____ kgs

B. Adverse event or product problem

1 ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)

☐ death ____ (mo/day/yr)

☐ life-threatening

☐ hospitalization – initial or prolonged

☐ disability

☐ congenital anomaly

☐ required intervention to prevent permanent impairment/damage

☐ other: ____

3 Date of event (mo/day/yr)

4 Date of this report (mo/day/yr)

5 Describe event or problem

6 Relevant tests/laboratory data, including dates

7 Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1 Name (give labeled strength & mfr/labeler, if known)

#1

#2

2 Dose, frequency & route used

#1

#2

3 Therapy dates (if unknown, give duration) from/to (or best estimate)

#1

#2

4 Diagnosis for use (indication)

#1

#2

5 Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6 Lot # (if known)

#1

#2

7 Exp. date (if known)

#1

#2

8 Event reappeared after reintroduction

#1 ☐ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9 NDC # (for product problems only)

____ - ____ - ____

10 Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1 Brand name

2 Type of device

3 Manufacturer name & address

4 Operator of device

☐ health professional

☐ lay user/patient

☐ other: ____

5 Expiration date (mo/day/yr)

6

model # ____

catalog # ____

serial # ____

lot # ____

other # ____

7 If implanted, give date (mo/day/yr)

8 If explanted, give date (mo/day/yr)

9 Device available for evaluation? (Do not send to FDA)

☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10 Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1 Name & address

phone #

2 Health professional?
☐ yes ☐ no

3 Occupation

4 Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5 If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

• 1-800-FDA-0178	to FAX report
• 1-800-FDA-7737	to report by modem
• 1-800-FDA-1088	to report by phone or for more information
• 1-800-822-7967	for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

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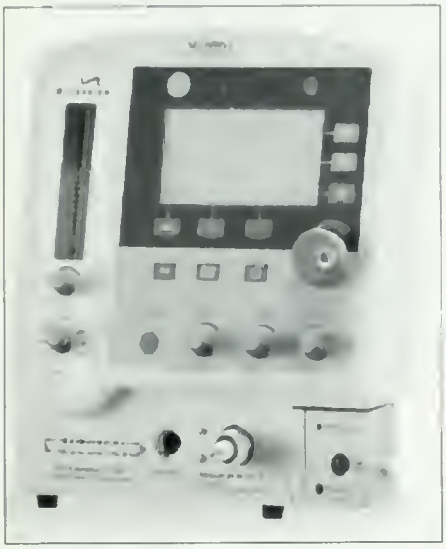
New Products & Services



Infant/Pediatric Ventilator. Sechrist Industries Inc has released its newest intensive care ventilator, the Millennium Infant/Pediatric Ventilator. A company press release says the new device is an electropneumatic, continuous-flow, time-cycled, pressure-limited ventilator intended for neonatal through pediatric use. The company also says the Millennium provides for assist/control, SIMV/IMV, CPAP, and CPAP with back-up ventilation as well as stand-by mode. Sechrist also provides Smart™, a feature the company describes as a sensitive trigger that serves as the sensor that facilitates assisted and synchronized ventilation, and also provides continuous feedback for the alarm and display systems. For more information from Sechrist Industries Inc circle number 187 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Inhalation Aerosol for Asthma. 3M Pharmaceuticals has recently acquired Food and Drug Administration approval for QVAR™ (beclomethasone dipropionate HFA) to be used in the treatment of asthma. According to 3M, this new metered-dose inhaler contains beclomethasone dipropionate (BDP) in a solution with no chlorofluorocarbon propellant. The company calls QVAR the first inhaler drug tailored to deliver small-particle-sized medication to the large, intermediate, and small airways. 3M says QVAR improves asthma control at a lower dose than conventional CFC-containing BDP inhalers. For more information from 3M Pharmaceuticals, circle number 188 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Fluid Warming Device. Futuremed America Inc has introduced the Astotherm Dry Heat Blood & I.V. Fluid Warmer. According to Futuremed, Astotherm technology has been successfully used in dialysis, hemofiltration, and urology, and is now being introduced for applications in the operating room, emergency room, and recovery room for warming blood and I.V. fluids. A company press announcement says the device has a large, real-time digital display for temperature monitoring and that it has three separate safety circuits, including alarms and a circuitry shutdown to guard against overheating. The company says it offers three models of the Astotherm and that they all provide easy setup and 60-second warming time. For more information from Futuremed America Inc, circle number 189 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Infant NCPAP. Hamilton Medical Inc has released the Arabella active NCPAP System for small infant and pediatric patients. According to the company, this new system provides safe and effective delivery of NCPAP using the patented Universal Generator, which incorporates fluidic principles of operation and reducing the work of breathing while maintaining a stable NCPAP level for infants. Hamilton says the Arabella uses a monitoring gas mixer that incorporates adjustable oxygen control, display of the analyzed gas and delivered NCPAP along with improved alarm functions. For more information from Hamilton Medical Inc, circle number 190 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

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Calendar of Events

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Date	AARC & Affiliates Programs	Contact
Feb. 7-9, 2001	10th Annual Winter Meeting; **Davis, WV**	WVSRS: Jay Wildt, (304) 442-7474, jay.wildt@mghwv.org or Anna Parkman (304) 357-4837, aparkman@ucwv.edu
March 14–16	22nd Annual Tahoe Conference, **Lake Tahoe, CA**	CSRC Greater Bay Area Chapter, (925) 866-6643; www.cssrc.org
April 4–5	USRC 2001 Conference; **Ogden, UT**	Utah Society for Respiratory Care, peberele@weber.edu
April 19–20	PSRC 4th Annual Eastern Regional Conference and Exhibition, **King of Prussia, PA**	Pennsylvania Society for Respiratory Care, Ann Cusano, (215) 646-7300, ext. 428, cusano.a@gmc.edu
Dec. 1-4, 2001	47th International Respiratory Congress; **San Antonio, TX**	AARC, (972) 243-2272, clay@aarc.org

Date	Other Meetings	Contact
Feb. 11–14	Cardiopulmonary Wellness & Rehabilitation meeting; **Telluride, CO**	American College of Chest Physicians, John Stangel, (847) 498-1400
March 7-9	8th International Conference on Home Mechanical Ventilation; **Lyon, France**	JIVD: Brigitte Hautier, +33 (0)4 78 39 08 43, brigitteHautier_JIVD@compuserve.com, www.jivd-france.com
March 29–30	Southern Maine Sleep Awareness Conference, **Portland, ME**	Diagnostic Health Services, Inc., Richard Haslip, (207) 781-9030, fax (207) 781-9031, RHSLEEP@Cybertours.com

Call for Abstracts
2001 RESPIRATORY CARE OPEN FORUM

Early Deadline: May 31, 2001
Final Deadline: July 17, 2001

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593

Scheduled Professor's Rounds 2001

Program #1 Taking the Mystery Out of Ventilator Weaning for Children—Peter Betit BS RRT FAARC; Host Richard D Branson BA RRT FAARC—Video March 13 Audio April 10

Program #2 Pulmonary Rehabilitation: Standard Care for Chronic Lung Disease Patients—Trina Limberg BS RRT; Host Thomas J Kallstrom RRT FAARC—Video March 27 Audio April 17

Program #3 Noninvasive Ventilation: The Latest Word—Dean R Hess PhD RRT FAARC; Host Richard D Branson BA RRT FAARC—Video April 24 Audio May 29

Program #4 Patient Education for the Asthmatic—Tracey Mitchell RRT; Host Thomas J Kallstrom RRT FAARC—Video May 22 Audio June 19

Program #5 ARDS: The Disease and Its Management—Leonard D Hudson MD; Host David J Pierson MD FAARC—Video June 26 Audio July 17

Program #6 New Respiratory Drugs: What, When, and How—Joseph L Rau PhD RRT FAARC; Host Patrick J Dunne MEd RRT FAARC—Video August 14 Audio September 11

Program #7 Invasive Ventilation: The Latest Word—Richard H Kallet MS RRT; Host Richard D Branson BA RRT FAARC—Video September 25 Audio October 16

Program #8 Test Your Lungs-Know Your Numbers-Prevent Emphysema—Thomas L Petty MD FAARC; Host David J Pierson MD FAARC—Video October 23 Audio November 20

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- Current job listings
- American Respiratory Care Foundation fellowships, grants, & awards
- Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- Subject and Author Indexes
- Contact the editorial staff
- OPEN FORUM; submit your abstract online

Asthma Management Model System
http://www.nhlbi.nih.gov

Keys to Professional Excellence
http://www.aarc.org/keys/

Committee on Accreditation for Respiratory Care
http://www.coarc.com

The National Board for Respiratory Care—Examination Fees for 2001

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Perinatal/Pediatric	$250 (new applicant) $220 (reapplicant)
CPFT	$200 (new applicant) $170 (reapplicant)
RPFT	$250 (new applicant) $220 (reapplicant)
RRT (Written & CSE)	$190 (new) $150 (reapplicant) written only $200 (new and reapplicant) CSE only $390 (new) $350 (reapplicant) both

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: nbrc-info@nbrc.org

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Ingmar	Neonatal Lung Model	119	800-583-9910	14
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MANUSCRIPTS. The Journal publishes clinical studies, method/device evaluations, reviews, and other materials related to cardiopulmonary medicine and research. Manuscripts may be submitted to the Editorial Office, RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Instructions for authors are printed in every issue. An expanded version of the Instructions is available from the editorial office.

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